

# ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BLyS

## **INTRODUCTION**

**[001]** The present invention relates to antibodies and related molecules that immunospecifically bind to BLyS. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS function or BLyS receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS.

## **BACKGROUND OF THE INVENTION**

**[002]** B lymphocyte stimulator (BLyS) is a member of the tumor necrosis factor ("TNF") superfamily that induces both *in vivo* and *in vitro* B cell proliferation and differentiation (Moore *et al.*, Science 285: 260-263 (1999)). BLyS is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLyS expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. BLyS expression on resting monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding BLyS has been mapped to chromosome 13q34.

**[003]** BLyS is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore *et al.*, 1999 *supra*). The membrane-bound form of BLyS has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH<sub>2</sub>-terminus of the soluble form of BLyS

begins at Ala<sup>134</sup> of the membrane-bound form of BLyS. Soluble recombinant BLyS has been shown to induce *in vitro* proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore *et al.*, 1999 *supra*). Soluble BLyS administration to mice has been shown to result in an increase in the proportion of CD45R<sup>dull</sup>, Ly6D<sup>bright</sup> (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore *et al.*, 1999 *supra*). Thus, BLyS displays a B cell tropism in both its receptor distribution and biological activity.

**[004]** Based upon its expression pattern and biological activity, BLyS has been suggested to be involved in the exchange of signals between B cells and monocytes or their differentiated progeny. The restricted expression patterns of BLyS receptor and ligand suggest that BLyS may function as a regulator of T cell-independent responses in a manner analogous to that of CD40 and CD40L in T cell-dependent antigen activation. As such, antibodies and related molecules that immunospecifically bind to BLyS may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes.

## **SUMMARY OF THE INVENTION**

**[005]** The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (*e.g.*, the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes), preferably human BLyS. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate function of

BLyS or BLyS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

**[0066]** Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to BLyS, including scFvs that immunospecifically bind to soluble BLyS, scFvs that immunospecifically bind the membrane-bound form of BLyS, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of BLyS. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (*e.g.*, including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the

soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[007] In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 – 2128, preferably SEQ ID NOS:834 - 872, 1570 - 1595, and 1886 – 1908, and most preferably SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, and 1881 - 1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1569, preferably SEQ ID NOS:1570 - 1595, and most preferably SEQ ID NOS: 1563 – 1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128, preferably SEQ ID NOS:1886 - 1908, and most preferably SEQ ID NOS: 1881 - 1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562, preferably SEQ ID NOS: 834 - 872, and most preferably SEQ ID NOS: 1 – 46, and 321 - 329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[008] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy (“VH”) domains referred to in Table 1, below, or any one of the variable light (“VL”) domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a



polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

**[009]** The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the

soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

**[010]** The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one, two, three or more of the VH complementarity determining regions (“CDRs”) (*i.e.*, VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (*i.e.*, VL CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (*e.g.*, including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

**[011]** In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, and comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, any

one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that correspond to the same scFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

**[012]** The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospecifically bind to the soluble form of BLyS (e.g., a polypeptide consisting of amino acids 134 - 285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of BLyS (e.g., a polypeptide consisting of amino acids 1 - 285 of SEQ ID NO:3228 or a BLyS polypeptide expressed on the surface of monocytes) and/or that immunospecifically bind to both the soluble form and membrane-bound form of BLyS. In a preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the soluble form of BLyS. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of BLyS. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL

CDR3 corresponding to one or more scFvs, that immunospecifically binds to the soluble form and membrane-bound form of BLyS. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, or both the soluble form and membrane-bound form of BLyS. Nucleic acid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

**[013]** A VH domain of an amino acid sequence disclosed herein may be combined with

**[014]** a VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains. Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed *infra*.

**[015]** The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to BLyS (e.g., soluble BLyS and membrane-bound BLyS) and can be routinely assayed for immunospecific binding to BLyS using methods known in the art, such as, for example, the immunoassays disclosed *infra*. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDR's. The antibodies of the invention (including antibody fragments, and variants

and derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs, VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention.

**[016]** The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')<sub>2</sub> fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')<sub>2</sub> fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs)). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

**[017]** The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the

invention.

**[018]** The present invention also provides for a nucleic acid molecule, generally

**[019]** isolated, encoding an antibody (including molecules such as scFvs, which comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

**[020]** The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

**[021]** In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (*e.g.*, AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (*e.g.*, an immunodeficiency).

**[022]** The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal,

preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[023] In specific embodiments, the present invention encompasses methods and compositions (*e.g.*, antagonistic anti-BLyS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (*e.g.*, AIDS, autoimmune diseases, and some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (*e.g.*, agonistic anti-BLyS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (*e.g.*, an immunodeficiency syndrome).

[024] Autoimmune diseases, conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (*e.g.*, IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (*e.g.*, Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (*i.e.*, Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c)

insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

[025] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

## **DEFINITIONS**

[026] The term "antibody," as used herein, refers to immunoglobulin molecules



and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragments. Examples of molecules which are described by the term “antibody” in this application include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab’ fragments, F(ab’)<sub>2</sub>, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term “single chain Fv” or “scFv” as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to BLyS may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to BLyS do not cross-react with other antigens. Antibodies that immunospecifically bind to BLyS can be identified, for example, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

**[027]** Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab’) fragments, antiidiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or subclass of immunoglobulin molecule.

**[028]** Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof.

**[029]** An antibody of the invention “which binds the soluble form of BLyS” is one which binds the 152 amino acid soluble form of the BLyS protein (amino acids 134-285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention “which binds the soluble form of BLyS” does not also bind the membrane-bound or membrane-associated form of BLyS. Assays which measure binding to the soluble form of BLyS include, but are not limited to, receptor binding inhibition assay or capture of soluble BLyS from solution as described in Examples 8 and 9.

**[030]** An antibody of the invention “which binds the membrane-bound form of

BLyS” is one which binds the membrane-associated (uncleaved) BLyS protein. In specific embodiments of the invention, an antibody of the invention “which binds the membrane-bound form of BLyS” does not also bind the soluble form of BLyS. Binding to HIS-tagged BLyS (as described herein) in an ELISA is an indicator that an antibody binds the membrane-bound form of BLyS, but should not be relied upon as proof of specificity for the membrane-bound form of BLyS. Assays that may be relied upon as proof of an antibody’s specificity for membrane-bound BLyS, include, but are not limited to, binding to plasma membranes expressing BLyS as described in Example 2. An antibody of the invention “which binds the both the soluble form and the membrane-bound form of BLyS” is one which binds both the membrane-bound form and the soluble form of BLyS.

**[031]** The term “variant” as used herein refers to a polypeptide that possesses a similar or identical function as a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, but does not necessarily comprise a similar or identical amino acid sequence of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, or possess a similar or identical structure of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof. A variant having a similar amino acid refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence encoding a BLyS polypeptide (e.g., SEQ ID NO:3228), a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at

least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein. A polypeptide with similar structure to a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

**[032]** To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

**[033]** The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and

BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410(1990) have incorporated such an algorithm. BLAST nucleotide searches can be performed with the BLASTn program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3389-3402(1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (e.g., BLASTx and BLASTn) can be used. (See <http://www.ncbi.nlm.nih.gov>.)

**[034]** Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci.*, 10 :3-5(1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8(1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

**[035]** The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a BLyS polypeptide, a fragment of BLyS, or an antibody of the invention that immunospecifically binds to BLyS, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a BLyS polypeptide, a fragment of BLyS, an antibody that immunospecifically binds to BLyS which has been modified, e.g., by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, may be modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS

antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, described herein.

**[036]** The term "epitopes" as used herein refers to portions of BLyS having antigenic or immunogenic activity in an animal, preferably a mammal. An epitope having immunogenic activity is a portion of BLyS that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of BLyS to which an antibody immunospecifically binds as determined by any method known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

**[037]** The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of BLyS, or an anti-BLyS antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically binds to BLyS.

**[038]** The term "fusion protein" as used herein refers to a polypeptide that comprises, or alternatively consists of, an amino acid sequence of an anti-BLyS antibody of the invention and an amino acid sequence of a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain).

**[039]** The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid

molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

### **DESCRIPTION OF THE FIGURES**

**[040]** Figure 1. ELISA results for three scFvs, I006E07, I008D05 and I016F04, that immunospecifically bind to U937 membranes, but not to bind to or cross-react with TNF-alpha or BSA.

**[041]** Figure 2. The results for three scFvs, I016H07, I001C09 and I018D07, in a receptor inhibition assay.

**[042]** Figure 3. ELISA results for two scFvs (I022D01 and I031F02) demonstrating their ability to bind to human BLyS and to cross-react with mouse BLyS, but not to bind to or cross-react with other antigens of the TNF ligand family.

**[043]** Figure 4. ELISA results for three scFvs (I031F09, I050A12, and I051C04) binding to U937 plasma membranes when either BLyS or TNF-alpha is used as a competitor.

**[044]** Figure 5. Kinetic analysis of scFv antibody I003C02. A dilution series of I003C02 from 3nM to 825nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

**[045]** Figure 6. Typical titration curves for two scFv antibodies (I007F11 and I050A07) are shown in Figure 6. Unlabelled BLyS competed for binding to its receptor with an IC<sub>50</sub> value of 0.8 nM. The IC<sub>50</sub> values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

**[046]** Figure 7. ELISA results for three scFvs clones (I074B12, I075F12 and I075A02) that immunospecifically bind to immobilized BLyS, but not to U937 plasma membranes, TNF-alpha or BSA. As a control, a phage antibody that recognizes TNF $\alpha$ , is also shown in Figure 7.

**[047]** Figure 8. The results for two scFvs (I025B09 and I026C04) in a receptor inhibition assay.

**[048]** Figure 9. ELISA results for two scFvs clones (I067F05 and I078D02) demonstrating their ability to bind to immobilized human BLyS and to cross-react with

immobilized mouse BLyS, but not to bind to or cross-react with other antigens of the TNF ligand family.

**[049]** As a control, a phage antibody that recognizes TNF $\alpha$ , is also shown in Figure 7.

**[050]** Figure 10. Kinetic analysis of scFV antibody I002A01. A dilution series of I002A01 from 3nM to 1650nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

**[051]** Figure 11. Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLyS competed for binding to its receptor with an inhibitory constant 50 (IC<sub>50</sub>) value of 0.66 nM. The IC<sub>50</sub> values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

**[052]** Figure 12. ELISA results for three clones (I079C01, I081C10 and I082A02) demonstrating their ability to bind histidine-tagged BLyS, U937 plasma membranes, but not to bind immobilized biotinylated BLyS.

**[053]** Figure 13. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to U937 plasma membranes when either histidine-tagged BLyS or biotinylated BLyS is used as a competitor.

**[054]** Figure 14. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in Figure 14. An anti-TNF $\alpha$  antibody that does not recognize BLyS was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

**[055]** Figure 15. A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as  $2 \times 10^{-3} \text{ s}^{-1}$ . The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv.

**[056]** Figure 16. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to P388 plasma membranes when either histidine-tagged BLyS or biotinylated BLyS is used as a competitor.

## **DETAILED DESCRIPTION OF THE INVENTION**

**[057]** The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS or a fragment or variant of BLyS. In particular, the invention provides antibodies such as, for example, single chain Fvs (scFvs) having an amino acid sequence of any one of SEQ ID NOS:1 - 2128, as referred to in Table 1. In particular, the present invention encompasses antibodies that immunospecifically bind to a polypeptide, a polypeptide fragment or variant, or an epitope of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes) (as determined by immunoassays known in the art for assaying specific antibody-antigen binding).

**[058]** The polypeptide sequence shown in SEQ ID NO:3228 was obtained by sequencing and translating the cDNA of the HNEDU15 clone which was deposited on October 22, 1996 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and assigned ATCC Accession No. 97768. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

**[059]** The polypeptide sequence shown in SEQ ID NO:3229 was obtained by sequencing and translating the cDNA of the HDPMC52 clone, which was deposited on December 10, 1998 at the American Type Culture Collection, and assigned ATCC Accession No. 203518. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

**[060]** The BLyS polypeptides bound by the antibodies of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to antibodies that bind monomers and multimers



of the BLyS polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind BLyS monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least trimers, or at least tetramers of BLyS.

**[061]** Multimeric BLyS bound by the antibodies of the invention may be homomers or heteromers. A BLyS homomer, refers to a multimer containing only BLyS polypeptides (including BLyS fragments, variants, and fusion proteins, as described herein). These homomers may contain BLyS polypeptides having identical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a BLyS homodimer (e.g., containing two BLyS polypeptides having identical or different amino acid sequences) or a BLyS homotrimer (e.g., containing three BLyS polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of BLyS. In additional embodiments, the antibodies of the invention bind a homomeric BLyS multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

**[062]** Heteromeric BLyS refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the BLyS polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a BLyS heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric BLyS multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both BLyS polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one BLyS polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising two BLyS polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention

contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

**[063]** In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, BLyS polypeptides, wherein the individual protein components of the multimers consist of the mature form of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, BLyS polypeptides such as a heterotrimer containing two BLyS polypeptides and one APRIL polypeptide or a heterotrimer containing one BLyS polypeptide and two APRIL polypeptides, and wherein the individual protein components of the BLyS heteromer consist of the mature extracellular soluble portion of either BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino acid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

**[064]** In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS monomeric protein. In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of BLyS with a heterologous polypeptide, such as might be present when BLyS forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID NO:3239)), or in fusion proteins between BLyS and a heterologous polypeptide.

**[065]** BLyS multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, BLyS multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, BLyS heteromultimers, such as, for example, BLyS heterotrimers or BLyS heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, BLyS multimers are formed

by covalent associations with and/or between the BLyS polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a BLyS fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a BLyS-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or BLyS polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple BLyS polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

**[066]** In one embodiment, antibodies of the invention immunospecifically bind a BLyS polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCC No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated BLyS polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCC No. 203518, or an antibody that binds polypeptide comprising a portion (i.e., fragment) of the above polypeptides.

**[067]** Antibodies of the present invention immunospecifically bind to

polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

**[068]** Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

**[069]** In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

**[070]** In specific embodiments, the antibodies of the present invention immunospecifically bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover,

polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

**[071]** In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228.

**[072]** It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a BLYS polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the BLYS polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the observed biological activities of the BLYS polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the BLYS polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the BLYS polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind BLYS polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

**[073]** Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino

acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

**[074]** Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of BLyS (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of BLyS (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of BLyS (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

**[075]** Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of BLyS (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of BLyS (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain of BLyS (amino acids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

**[076]** Certain additional embodiments of the invention encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the BLyS polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of BLyS comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of BLyS comprise, or alternatively consist

of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

**[077]** A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acids sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of (SEQ ID NO:3228). Other combinations of amino acids sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag ; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

**[078]** A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused

to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229.

**[079]** Additional embodiments of the invention encompass antibodies that bind BLyS polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 and as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of a complete (i.e., full-length) BLyS polypeptide (e.g., SEQ ID NOS:3228 and 3229).

**[080]** The data representing the structural or functional attributes of the BLyS polypeptide of SEQ ID NO:3228 (Table 9) or the BLyS polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a



Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

**[081]** In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the BLyS polypeptide of SEQ ID NO:3228 (Table 9) or the BLyS polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

**[082]** The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Preferably, antibodies of the present invention bind BLyS polypeptides or BLyS polypeptide fragments and variants comprising regions of BLyS that combine several structural features, such as several (e.g., 1, 2, 3, or 4) of the same or different region features set out above and in Tables 9 and 10.

Table 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	.	.	.	.	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	.	.	.	.	.	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	.	.	.	.	.	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	.	.	.	.	.	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	.	.	.	.	.	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	.	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	.	.	.	.	.	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	.	.	.	.	.	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	.	.	.	.	.	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	.	.	.	.	.	1.32	-1.74	.	.	F	0.90	4.44
Arg	19	A	A	.	.	.	.	.	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	.	.	.	.	.	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	.	.	.	.	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	.	.	.	.	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	.	.	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	.	.	.	.	.	T	.	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	.	.	.	.	.	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	.	.	.	.	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	.	.	.	.	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	.	*	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	.	.	.	.	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	.	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	.	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	.	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	.	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	.	.	.	.	T	.	-0.50	0.16	.	*	.	0.10	0.55
Gln	73	A	.	.	.	.	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	.	.	.	.	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	.	.	.	.	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	.	.	.	.	.	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	.	*	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	.	.	.	.	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	.	.	.	.	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	.	.	.	.	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	.	.	.	.	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	*	F	F	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	.	F	0.60	1.01

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	.	*	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	.	.	.	.	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	.	.	.	.	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	.	.	.	.	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	.	.	.	.	.	.	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	.	.	.	.	.	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	.	.	.	.	.	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	.	.	.	.	T	T	.	1.29	-0.39	.	.	F	2.15	0.98
Glu	122	.	.	.	.	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	.	.	.	.	.	.	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	.	.	.	.	.	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	.	.	.	.	.	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	.	.	.	.	.	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	.	.	.	.	.	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	.	.	.	.	.	.	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	.	.	.	.	.	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	.	.	.	.	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	.	.	.	.	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	.	.	.	.	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	.	.	.	.	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	.	.	.	.	.	.	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	.	.	.	.	.	T	C	1.30	-0.60	*	.	F	2.52	1.35
Pro	138	.	.	.	.	.	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	.	.	.	.	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	.	.	.	.	T	.	1.47	-0.53	*	.	F	2.66	1.64
Thr	141	A	.	.	.	.	.	.	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	.	.	.	.	.	.	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	.	.	.	.	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	.	.	.	.	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	.	.	.	.	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	.	.	.	.	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	.	.	.	.	.	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	.	.	.	.	.	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	.	.	.	.	.	-0.57	0.53	*	*	.	-0.30	0.32
Ile	150	A	A	.	.	.	.	.	-0.57	0.34	*	.	.	0.30	0.52

Table 9 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala 151	.	A	.	.	.	.	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp 152	.	.	.	.	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser 153	.	.	.	.	.	T	C	0.08	-0.51	.	.	F	3.00	2.00
Glu 154	.	.	.	.	.	T	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr 155	.	.	.	.	.	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro 156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr 157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile 158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln 159	.	.	.	.	T	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys 160	.	.	.	.	T	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly 161	.	.	.	.	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser 162	.	.	.	.	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr 163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr 164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe 165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val 166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro 167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp 168	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu 169	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu 170	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ter 171	A	.	.	.	.	.	.	0.19	0.46	*	.	.	0.20	0.71
Phe 172	.	.	.	.	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys 173	.	.	.	.	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg 174	.	.	.	.	.	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly 175	.	.	.	.	.	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser 176	A	.	.	.	.	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala 177	A	A	.	.	.	.	.	1.66	-1.00	*	.	F	1.35	0.76
Leu 178	A	A	.	.	.	.	.	1.61	-1.00	.	.	F	1.20	1.54
Glu 179	A	A	.	.	.	.	.	1.50	-1.43	.	.	F	0.90	1.98
Glu 180	A	A	.	.	.	.	.	1.89	-1.41	*	.	F	0.90	3.16
Lys 181	A	A	.	.	.	.	.	1.30	-1.91	*	.	F	0.90	7.66
Glu 182	A	A	.	.	.	.	.	1.08	-1.91	.	.	F	0.90	3.10
Asn 183	A	A	.	.	.	.	.	1.03	-1.23	*	*	F	0.90	1.48
Lys 184	A	A	.	.	.	.	.	1.08	-0.59	*	*	F	0.75	0.55
Ile 185	A	A	.	.	.	.	.	1.08	-0.59	*	*	.	0.60	0.63
Leu 186	A	A	.	.	.	.	.	0.72	-0.59	*	*	.	0.60	0.68
Val 187	A	A	.	.	.	.	.	0.38	-0.50	*	*	.	0.30	0.49
Lys 188	A	A	.	.	.	.	.	0.13	-0.07	*	*	F	0.45	0.69
Glu 189	A	.	.	.	.	T	.	-0.61	0.00	*	*	F	0.40	1.32
Thr 190	.	.	.	.	T	T	.	-0.42	0.10	.	*	F	0.80	1.54
Gly 191	.	.	.	.	T	T	.	-0.50	0.24	*	.	F	0.65	0.67
Tyr 192	.	.	.	.	T	T	.	0.11	0.93	*	*	.	0.20	0.27
Phe 193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29
Phe 194	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.60	0.29
Ile 195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr 196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly 197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln 198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val 199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu 200	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Tyr	201	.	.	.	.	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	202	.	.	.	.	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	203	.	.	.	.	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	204	A	.	.	.	.	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	205	A	A	.	.	.	.	.	0.90	-0.16	.	.	F	0.60	1.73
Tyr	206	A	A	.	.	.	.	.	1.11	-0.21	.	.	.	0.45	1.03
Ala	207	A	A	.	.	.	.	.	0.61	0.29	.	.	.	-0.30	0.70
Met	208	A	A	.	.	.	.	.	-0.28	0.97	.	.	.	-0.60	0.40
Gly	209	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	210	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.30	0.61
Leu	211	A	A	.	B	.	.	.	0.39	0.31	.	.	.	0.45	1.22
Ile	212	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.75	1.80
Gln	213	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.90	1.62
Arg	214	A	A	.	B	.	.	.	1.08	-0.59	.	.	F	0.90	3.14
Lys	215	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	1.35
Lys	216	A	A	.	B	.	.	.	0.37	-0.81	*	*	F	0.90	1.35
Val	217	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	218	.	A	B	B	.	.	.	0.91	-0.00	*	*	.	0.30	0.29
Val	219	.	A	B	B	.	.	.	0.80	-0.00	*	*	.	0.30	0.25
Phe	220	.	.	B	B	.	.	.	-0.06	-0.00	*	.	.	0.30	0.57
Gly	221	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	222	A	.	.	.	.	.	.	-0.36	-0.07	*	.	.	0.50	0.63
Glu	223	A	.	.	.	.	.	.	-1.18	-0.03	*	.	.	0.50	0.60
Leu	224	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	225	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	226	A	.	.	B	.	.	.	-1.10	0.57	.	.	.	-0.60	0.18
Val	227	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	228	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	229	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	230	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	231	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	232	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	233	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	234	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	235	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	236	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	237	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	238	.	.	.	.	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	239	.	.	.	.	.	.	C	1.36	0.04	*	.	F	1.12	1.82
Leu	240	.	.	.	.	.	.	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	241	.	.	.	.	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	242	.	.	.	.	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	243	.	.	.	.	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	244	.	.	.	.	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	245	.	.	.	.	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	246	.	.	.	.	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	247	A	.	.	.	.	.	.	-0.42	0.71	.	.	.	-0.40	0.18
Ala	248	A	A	.	.	.	.	.	-0.38	0.83	.	.	.	-0.60	0.34
Gly	249	A	A	.	.	.	.	.	-0.89	0.26	.	.	.	-0.30	0.43
Ile	250	A	A	.	.	.	.	.	-0.22	0.19	*	.	.	-0.30	0.27

Table 9 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala 251	A	A	.	.	.	.	.	0.02	-0.20	*	.	.	0.30	0.46
Lys 252	A	A	.	.	.	.	.	-0.02	-0.70	.	.	.	0.60	0.80
Leu 253	A	A	.	.	.	.	.	0.57	-0.70	.	.	F	0.90	1.13
Glu 254	A	A	.	.	.	.	.	0.91	-1.39	.	.	F	0.90	1.87
Glu 255	A	A	.	.	.	.	.	0.99	-1.89	.	.	F	0.90	1.62
Gly 256	A	A	.	.	.	.	.	1.58	-1.20	.	*	F	0.90	1.62
Asp 257	A	A	.	.	.	.	.	0.72	-1.49	.	*	F	0.90	1.62
Glu 258	A	A	.	.	.	.	.	0.94	-0.80	*	*	F	0.75	0.77
Leu 259	A	A	.	.	.	.	.	0.06	-0.30	*	*	.	0.30	0.79
Gln 260	A	A	.	.	.	.	.	-0.16	-0.04	*	.	.	0.30	0.33
Leu 261	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.30
Ala 262	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.70
Ile 263	A	A	.	.	.	.	.	0.30	-0.30	.	*	.	0.30	0.70
Pro 264	A	.	.	.	.	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg 265	A	.	.	.	.	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu 266	A	.	.	.	.	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn 267	A	.	.	.	.	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala 268	A	.	.	.	.	.	.	0.81	-0.63	*	*	.	0.95	1.05
Gln 269	A	.	.	.	.	.	.	1.02	0.06	*	*	.	-0.10	0.50
Ile 270	A	.	.	.	.	.	.	0.57	0.06	.	*	.	0.15	0.52
Ser 271	.	.	.	.	.	.	C	0.57	0.09	.	*	.	0.60	0.51
Leu 272	.	.	.	.	.	.	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp 273	.	.	.	.	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly 274	.	.	.	.	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp 275	.	.	.	.	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val 276	A	.	.	.	.	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr 277	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe 278	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe 279	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly 280	A	A	.	.	.	.	.	-1.58	0.67	.	*	.	-0.60	0.28
Ala 281	A	A	.	.	.	.	.	-1.53	0.87	.	*	.	-0.60	0.27
Leu 282	A	A	.	.	.	.	.	-1.61	0.77	*	.	.	-0.60	0.26
Lys 283	A	A	.	.	.	.	.	-1.30	0.41	*	.	.	-0.60	0.33
Leu 284	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu 285	A	A	.	.	.	.	.	-1.03	0.34	*	.	.	-0.30	0.65

Table 10

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	.	.	.	.	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	.	.	.	.	.	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	.	.	.	.	.	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	.	.	.	.	.	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	.	.	.	.	.	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	.	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	.	.	.	.	.	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	.	.	.	.	.	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	.	.	.	.	.	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	.	.	.	.	.	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	.	.	.	.	.	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	.	.	.	.	.	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	.	.	.	.	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	.	.	.	.	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	.	.	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	.	.	.	.	.	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	.	.	.	.	.	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	.	.	.	.	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	.	.	.	.	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	*	*	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	.	.	.	.	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19



Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	.	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	.	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	.	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	.	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	*	.	.	-0.60	0.25
Leu	72	A	.	.	.	.	T	.	-0.50	0.16	.	.	.	0.10	0.55
Gln	73	A	.	.	.	T	.	.	-1.09	0.20	.	F	.	0.25	0.45
Gly	74	A	.	.	.	T	.	.	-0.53	0.20	.	F	.	0.25	0.45
Asp	75	A	.	.	.	T	.	.	-0.76	0.09	*	F	.	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	*	F	.	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	*	.	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	*	.	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	*	.	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	*	.	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	*	.	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	*	.	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	*	.	.	0.30	0.77
Gln	84	A	A	.	.	.	.	.	1.21	0.01	*	.	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	*	.	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	*	.	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	*	.	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	*	.	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	*	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	.	.	.	.	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	.	.	.	.	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	.	.	.	.	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	.	.	.	.	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	*	.	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	F	.	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	F	.	0.65	0.72
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	*	F	.	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	F	.	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	F	.	0.60	1.01

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	*	*	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	.	.	.	.	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	.	.	.	.	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	.	.	.	.	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	.	.	.	.	.	.	C	0.34	0.00	*	.	F	2.20	1.47
Ala	119	.	.	.	.	.	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	.	.	.	.	.	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	.	.	.	.	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	.	.	.	.	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	.	.	.	.	.	.	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	.	.	.	.	.	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	.	.	.	.	.	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	.	.	.	.	.	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	.	.	.	.	.	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	.	.	.	.	.	.	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	.	.	.	.	.	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	.	.	.	.	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	.	.	.	.	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	.	.	.	.	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	.	.	.	.	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	.	.	.	.	.	.	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.15	0.89
Gln	136	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.49	0.79
Gly	137	.	.	.	.	.	T	C	1.30	-0.60	*	.	F	2.18	1.35
Pro	138	.	.	.	.	.	T	C	0.84	-0.61	*	.	F	2.52	2.63
Glu	139	.	.	.	.	.	T	C	1.13	-0.83	*	.	F	2.86	1.50
Glu	140	.	.	.	.	T	T	.	1.74	-0.84	.	.	F	3.40	2.03
Thr	141	.	.	.	.	T	.	.	1.43	-0.51	.	.	F	2.86	2.06
Gly	142	.	.	.	.	T	T	.	1.08	-0.46	.	.	F	2.42	1.72
Ser	143	.	.	.	.	T	T	.	0.43	0.33	.	.	F	1.33	0.86
Tyr	144	.	.	.	.	T	T	.	0.22	0.97	.	.	.	0.54	0.44
Thr	145	.	.	.	.	T	T	.	-0.07	0.91	.	.	.	0.20	0.69
Phe	146	.	.	B	B	.	.	.	-0.57	1.40	.	.	.	-0.60	0.54
Val	147	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	148	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	149	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	150	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Leu	151	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ser	152	A	.	.	.	.	.	.	0.19	0.46	*	.	.	0.20	0.71
Phe	153	.	.	.	.	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	154	.	.	.	.	T	.	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	155	.	.	.	.	.	T	C	-0.20	-0.51	*	.	F	3.00	1.04
Gly	156	.	.	.	.	.	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	157	A	.	.	.	.	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	158	A	A	.	.	.	.	.	1.66	-1.00	*	.	F	1.35	0.76
Leu	159	A	A	.	.	.	.	.	1.61	-1.00	.	.	F	1.20	1.54
Glu	160	A	A	.	.	.	.	.	1.50	-1.43	.	.	F	0.90	1.98
Glu	161	A	A	.	.	.	.	.	1.89	-1.41	*	.	F	0.90	3.16
Lys	162	A	A	.	.	.	.	.	1.30	-1.91	*	.	F	0.90	7.66
Glu	163	A	A	.	.	.	.	.	1.08	-1.91	*	.	F	0.90	3.10
Asn	164	A	A	.	.	.	.	.	1.03	-1.23	*	*	F	0.90	1.48
Lys	165	A	A	.	.	.	.	.	1.08	-0.59	*	.	F	0.75	0.55
Ile	166	A	A	.	.	.	.	.	1.08	-0.59	*	.	.	0.60	0.63
Leu	167	A	A	.	.	.	.	.	0.72	-0.59	*	*	.	0.76	0.68
Val	168	A	A	.	.	.	.	.	0.38	-0.50	.	.	.	0.92	0.49
Lys	169	A	A	.	.	.	.	.	0.13	-0.07	*	*	F	0.93	0.69
Glu	170	A	.	.	.	.	T	.	-0.61	0.00	*	*	F	1.64	1.32
Thr	171	.	.	.	.	T	T	.	-0.42	0.10	.	*	F	1.60	1.54
Gly	172	.	.	.	.	T	T	.	-0.50	0.24	*	.	F	1.29	0.67
Tyr	173	.	.	.	.	T	T	.	0.11	0.93	*	*	.	0.68	0.27
Phe	174	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.28	0.29
Phe	175	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.44	0.29
Ile	176	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	177	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	178	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	179	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	180	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	181	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92
Tyr	182	.	.	.	.	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	183	.	.	.	.	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	184	.	.	.	.	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	185	A	.	.	.	.	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	186	A	A	.	.	.	.	.	0.90	-0.16	.	.	F	0.60	1.73
Tyr	187	A	A	.	.	.	.	.	1.11	-0.21	.	.	.	0.45	1.03
Ala	188	A	A	.	.	.	.	.	0.61	0.29	.	.	.	-0.30	0.70
Met	189	A	A	.	.	.	.	.	-0.28	0.97	.	.	.	-0.60	0.40
Gly	190	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	191	A	A	.	B	.	.	.	0.10	-0.81	*	.	.	-0.60	0.31
Leu	192	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	193	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	194	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	195	A	A	.	B	.	.	.	1.08	-0.59	*	*	F	0.90	1.62
Lys	196	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	197	A	A	.	B	.	.	.	0.37	-0.81	*	*	F	0.90	1.35
Val	198	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	199	.	A	B	B	.	.	.	0.91	0.00	*	*	.	0.30	0.29
Val	200	.	A	B	B	.	.	.	0.80	0.00	*	*	.	0.30	0.25

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Phe	201	.	.	B	B	.	.	.	-0.06	0.00	*	.	.	0.30	0.57
Gly	202	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	203	A	.	.	.	.	.	.	-0.36	-0.07	*	.	.	0.50	0.63
Glu	204	A	.	.	.	.	.	.	-1.18	-0.03	*	.	.	0.50	0.60
Leu	205	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	206	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	207	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	208	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	209	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	210	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	211	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	212	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	213	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	214	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	215	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	216	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	217	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	218	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	219	.	.	.	.	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	220	.	.	.	.	.	.	C	1.36	0.04	*	.	F	1.12	1.82
Leu	221	.	.	.	.	.	.	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	222	.	.	.	.	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	223	.	.	.	.	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	224	.	.	.	.	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	225	.	.	.	.	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	226	.	.	.	.	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	227	.	.	.	.	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	228	A	.	.	.	.	.	.	-0.42	0.71	.	.	.	-0.40	0.18
Ala	229	A	A	.	.	.	.	.	-0.38	0.83	.	.	.	-0.60	0.34
Gly	230	A	A	.	.	.	.	.	-0.89	0.26	.	.	.	-0.30	0.43
Ile	231	A	A	.	.	.	.	.	-0.22	0.19	*	.	.	-0.30	0.27
Ala	232	A	A	.	.	.	.	.	0.02	-0.20	*	.	.	0.30	0.46
Lys	233	A	A	.	.	.	.	.	-0.02	-0.70	.	.	.	0.60	0.80
Leu	234	A	A	.	.	.	.	.	0.57	-0.70	.	.	F	0.90	1.13
Glu	235	A	A	.	.	.	.	.	0.91	-1.39	.	.	F	0.90	1.87
Glu	236	A	A	.	.	.	.	.	0.99	-1.89	.	.	F	0.90	1.62
Gly	237	A	A	.	.	.	.	.	1.58	-1.20	.	*	F	0.90	1.62
Asp	238	A	A	.	.	.	.	.	0.72	-1.49	.	*	F	0.90	1.62
Glu	239	A	A	.	.	.	.	.	0.94	-0.80	*	*	F	0.75	0.77
Leu	240	A	A	.	.	.	.	.	0.06	-0.30	*	*	.	0.30	0.79
Gln	241	A	A	.	.	.	.	.	-0.16	-0.04	*	.	.	0.30	0.33
Leu	242	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.30
Ala	243	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.70
Ile	244	A	A	.	.	.	.	.	0.30	-0.30	.	*	.	0.30	0.70
Pro	245	A	.	.	.	.	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	246	A	.	.	.	.	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	247	A	.	.	.	.	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	248	A	.	.	.	.	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	249	A	.	.	.	.	.	.	0.81	-0.63	*	*	.	0.95	1.05
Gln	250	A	.	.	.	.	.	.	1.02	0.06	*	*	.	-0.10	0.50

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ile	251	A	.	.	.	.	.	.	0.57	0.06	*	*	.	0.15	0.52
Ser	252	.	.	.	.	.	.	C	0.57	0.09	.	*	.	0.60	0.51
Leu	253	.	.	.	.	.	.	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	254	.	.	.	.	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	255	.	.	.	.	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	256	.	.	.	.	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	257	A	.	.	.	.	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	261	A	A	.	.	.	.	.	-1.58	0.67	.	*	.	-0.60	0.28
Ala	262	A	A	.	.	.	.	.	-1.53	0.87	.	*	.	-0.60	0.27
Leu	263	A	A	.	.	.	.	.	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	.	.	.	.	.	-1.30	0.41	*	.	.	-0.60	0.33
Leu	265	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	.	.	.	.	.	-1.03	0.34	*	.	.	-0.30	0.65

**[083]** In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983).

**[084]** As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science*, 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson *et al.*, *Cell* 37:767-778 (1984) at 777.

**[085]** In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of BLyS and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a BLyS polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

**[086]** Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLyS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-171 to about Phe-194 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in Figures 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLyS polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

**[087]** Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLyS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLyS polypeptide by the analysis of the Jameson-Wolf

antigenic index, as disclosed in Table 10 generated by the Protean component of the DNA\*STAR computer program (as set forth above).

[088] BLYS epitope-bearing peptides and polypeptides may be produced by any conventional means. *See, e.g.,* Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA* 82:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U. S. Patent No. 4,631,211 to Houghten et al. (1986).

[089] The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 97768, or encoded by a polynucleotide that hybridizes to cDNA sequence contained in ATCC deposit No. 97768 (e.g., under hybridization conditions described herein).

[090] The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCC deposit No. 203518 (e.g., under hybridization conditions described herein).

[091] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not



necessarily be immunogenic.

**[092]** BLyS polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

**[093]** In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

**[094]** Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes of BLyS may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

**[095]** Epitope-bearing BLyS polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

**[096]** As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the BLyS polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of

mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

**[0997]** In another embodiment, the antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

**[0998]** In a more specific embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

**[0999]** In another embodiment, antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind BLyS polypeptides of the present invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

**[10100]** In another embodiment, antibodies of the present invention bind mutant

BLyS polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the BLyS polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of BLyS recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

**[0101]** In another preferred embodiment, antibodies of the present invention bind BLyS polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

**[0102]** To improve or alter the characteristics of BLyS polypeptides, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for many proteins, including the extracellular domain or the mature form(s) of a secreted

protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., J. Biol. Chem., 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind BLyS polypeptide mutants or variants generated by protein engineering.

**[0103]** In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

**[0104]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the BLyS of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues  $n^1$ -285 of SEQ ID NO:3228, where  $n^1$  is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group

consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285, 157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

**[0105]** Furthermore, since the predicted extracellular domain of the BLYS polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLYS polypeptide results

in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

**[0106]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues  $n^2$ -285 of SEQ ID NO:3228, where  $n^2$  is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285;

T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

**[0107]** Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an



amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

**[0108]** Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

**[0109]** Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

**[0110]** In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of BLYS: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

**[0111]** Similarly, many examples of biologically functional C-terminal deletion

polypeptides are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein (Döbeli et al., *J. Biotechnology* 7:199-216 (1988)). Since the present protein is a member of the TNF polypeptide family, deletions of C-terminal amino acids up to the leucine residue at position 284 are expected to retain most if not all biological activity such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication. Polypeptides having deletions of up to about 10 additional C-terminal residues (i.e., up to the glycine residue at position 274) also may retain some activity such as receptor binding, although such polypeptides would lack a portion of the conserved TNF domain which extends to about Leu-284 of SEQ ID NO:3228. However, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or mature protein generally will be retained when less than the majority of the residues of the complete or mature protein are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

**[0112]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS polypeptide of SEQ ID NO:3228, up to the glycine residue at position 274 (Gly-274). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m<sup>1</sup> of the amino acid sequence in SEQ ID NO:3228, where m<sup>1</sup> is any integer in the range of the amino acid position of amino acid residues 274-284 in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind BLyS polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 1-274, 1-275, 1-276, 1-277, 1-278, 1-279, 1-280, 1-281, 1-282, 1-283 and 1-284 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or



the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 73-m<sup>2</sup> of the amino acid sequence in SEQ ID NO:3228, where m<sup>2</sup> is any integer in the range of the amino acid position of amino acid residues 79 to 285 in the amino acid sequence in SEQ ID NO:3228, and residue 78 is the position of the first residue at the C- terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to Leu-285; Q-73 to L-284; Q-73 to K-283; Q-73 to L-282; Q-73 to A-281; Q-73 to G-280; Q-73 to F-279; Q-73 to F-278; Q-73 to T-277; Q-73 to V-276; Q-73 to D-275; Q-73 to G-274; Q-73 to D-273; Q-73 to L-272; Q-73 to S-271; Q-73 to I-270; Q-73 to Q-269; Q-73 to A-268; Q-73 to N-267; Q-73 to E-266; Q-73 to R-265; Q-73 to P-264; Q-73 to I-263; Q-73 to A-262; Q-73 to L-261; Q-73 to Q-260; Q-73 to L-259; Q-73 to E-258; Q-73 to D-257; Q-73 to G-256; Q-73 to E-255; Q-73 to E-254; Q-73 to L-253; Q-73 to K-252; Q-73 to A-251; Q-73 to I-250; Q-73 to G-249; Q-73 to A-248; Q-73 to S-247; Q-73 to Y-246; Q-73 to C-245; Q-73 to S-244; Q-73 to N-243; Q-73 to N-242; Q-73 to P-241; Q-73 to L-240; Q-73 to T-239; Q-73 to E-238; Q-73 to P-237; Q-73 to M-236; Q-73 to N-235; Q-73 to Q-234; Q-73 to I-233; Q-73 to C-232; Q-73 to R-231; Q-73 to F-230; Q-73 to L-229; Q-73 to T-228; Q-73 to V-227; Q-73 to L-226; Q-73 to S-225; Q-73 to L-224; Q-73 to E-223; Q-73 to D-222; Q-73 to G-221; Q-73 to F-220; Q-73 to V-219; Q-73 to H-218; Q-73 to V-217; Q-73 to K-216; Q-73 to K-215; Q-73 to R-214; Q-73 to Q-213; Q-73 to I-212; Q-73 to L-211; Q-73 to H-210; Q-73 to G-209; Q-73 to M-208; Q-73 to A-207; Q-73 to Y-206; Q-73 to T-205; Q-73 to K-204; Q-73 to D-203; Q-73 to T-202; Q-73 to Y-201; Q-73 to L-200; Q-73 to V-199; Q-73 to Q-198; Q-73 to G-197; Q-73 to Y-196; Q-73 to I-195; Q-73 to F-194; Q-73 to F-193; Q-73 to Y-192; Q-73 to G-191; Q-73 to T-190; Q-73 to E-189; Q-73 to K-188; Q-73 to V-187; Q-73 to L-186; Q-73 to I-185; Q-73 to K-184; Q-73 to N-183; Q-73 to E-182; Q-73 to K-181; Q-73 to E-180; Q-73 to E-179; Q-73 to L-178; Q-73 to A-177; Q-73 to S-176; Q-73 to G-175; Q-73 to R-174; Q-73 to K-173; Q-73 to F-172; Q-73 to S-171; Q-73 to L-170; Q-73 to L-169; Q-73 to W-168; Q-73 to P-167; Q-73 to V-166; Q-73 to F-165; Q-73 to T-164; Q-73 to Y-163; Q-73 to S-162; Q-73 to G-161; Q-73 to K-160; Q-73 to Q-159; Q-73 to I-158; Q-73 to T-157; Q-73 to P-156;

Q-73 to T-155; Q-73 to E-154; Q-73 to S-153; Q-73 to D-152; Q-73 to A-151; Q-73 to I-150; Q-73 to L-149; Q-73 to Q-148; Q-73 to L-147; Q-73 to C-146; Q-73 to D-145; Q-73 to Q-144; Q-73 to T-143; Q-73 to V-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; and Q-73 to L-79 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0117]** The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLyS, which may be described generally as having residues  $n^2$ - $m^2$  of SEQ ID NO:3228 where  $n^2$  and  $m^2$  are integers as defined above.

**[0118]** In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLyS amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, where this portion excludes from 1 to about 206 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, or from 1 to about 206 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the

cDNA plasmid contained in the deposit having ATCC accession no. 97768.

**[0119]** As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functions or biological activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

**[0120]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280 of the sequence shown SEQ ID NO:3228 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues  $n^3$ -285 of the sequence shown in SEQ ID NO:3228, where  $n^3$  is an integer in the range of the amino acid position of amino acid residues 1 to 280 of the amino acid sequence in SEQ ID NO:3228.

**[0121]** More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-285; D-3 to L-285; S-4 to L-285; T-5 to L-285; E-6 to L-285; R-7 to L-285; E-8 to L-285; Q-9 to L-285; S-10 to L-285; R-11 to L-285; L-12 to L-285; T-13 to L-285; S-14 to L-285; C-15 to L-285; L-16 to L-285; K-17 to L-285; K-18 to L-285; R-19 to L-285; E-20 to L-285; E-21 to L-285; M-22 to L-285; K-23 to L-285; L-24 to L-285; K-25 to L-285; E-26 to L-285; C-27 to L-285; V-28 to L-285; S-29 to L-285; I-30 to L-285; L-31 to L-285; P-32 to L-285; R-33 to L-285; K-34 to L-285; E-35

to L-285; S-36 to L-285; P-37 to L-285; S-38 to L-285; V-39 to L-285; R-40 to L-285; S-41 to L-285; S-42 to L-285; K-43 to L-285; D-44 to L-285; G-45 to L-285; K-46 to L-285; L-47 to L-285; L-48 to L-285; A-49 to L-285; A-50 to L-285; T-51 to L-285; L-52 to L-285; L-53 to L-285; L-54 to L-285; A-55 to L-285; L-56 to L-285; L-57 to L-285; S-58 to L-285; C-59 to L-285; C-60 to L-285; L-61 to L-285; T-62 to L-285; V-63 to L-285; V-64 to L-285; S-65 to L-285; F-66 to L-285; Y-67 to L-285; Q-68 to L-285; V-69 to L-285; A-70 to L-285; A-71 to L-285; L-72 to L-285; Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to

L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0122]** Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activity) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

**[0123]** Accordingly, the present invention further provides in another embodiment,



antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m<sup>3</sup> of SEQ ID NO:3228, where m<sup>3</sup> is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

**[0124]** More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to I-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to I-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to I-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to I-212; M-1 to L-211; M-1 to H-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to I-195; M-1 to F-194; M-1 to F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to I-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to I-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to I-150; M-1 to L-149; M-1 to

Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0125] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n<sup>3</sup>-m<sup>3</sup> of SEQ ID NO:3228, where n<sup>3</sup> and m<sup>3</sup> are integers as defined above.

**[0126]** Furthermore, since the predicted extracellular domain of the BLyS

polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Gln-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

**[0127]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues  $n^4$ -266 of SEQ ID NO:3229, where  $n^4$  is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain BLyS polypeptide (shown in SEQ ID NO:3229).

**[0128]** More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to

L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies

that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0129]** Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLyS up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

**[0130]** However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

**[0131]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLyS shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73-m<sup>4</sup> of the amino acid sequence in SEQ ID NO:3229, where m<sup>4</sup> is any integer in the range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

**[0132]** More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to

T-258; Q-73 to V-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253; Q-73 to S-252; Q-73 to I-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to I-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to I-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to I-214; Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-210; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to I-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to V-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177; Q-73 to I-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to I-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to

R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0133]** The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLyS, which may be described generally as having residues  $n^4$ - $m^4$  of SEQ ID NO:3229 where  $n^4$  and  $m^4$  are integers as defined above.

**[0134]** In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLyS amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518.

**[0135]** As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened BLyS polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six

BLYS amino acid residues may often evoke an immune response.

**[0136]** Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLYS polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n<sup>5</sup>-266 of the sequence shown in SEQ ID NO:3229, where n<sup>5</sup> is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

**[0137]** More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to



L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0138]** Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

**[0139]** Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m<sup>5</sup> of SEQ ID NO:3229, where m<sup>5</sup> is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

**[0140]** More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to I-251; M-1 to Q-250; M-1 to A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to I-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to G-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to I-214; M-1 to

C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to I-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to T-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to I-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to I-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15;

M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0141]** The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues  $n^5$ - $m^5$  of SEQ ID NO:3229, where  $n^5$  and  $m^5$  are integers as defined above.

**[0142]** In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134- $m^6$  of SEQ ID NO:3228, where  $m^6$  is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to I-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to



A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to V-142; S-129 to T-143; R-130 to Q-144; N-131 to D-145; K-132 to C-146; R-133 to L-147; A-134 to Q-148; V-135 to L-149; Q-136 to I-150; G-137 to A-151; P-138 to D-152; E-139 to S-153; E-140 to E-154; T-141 to T-155; V-142 to P-156; T-143 to T-157; Q-144 to I-158; D-145 to Q-159; C-146 to K-160; L-147 to G-161; Q-148 to S-162; L-149 to Y-163; I-150 to T-164; A-151 to F-165; D-152 to V-166; S-153 to P-167; E-154 to W-168; T-155 to L-169; P-156 to L-170; T-157 to S-171; I-158 to F-172; Q-159 to K-173; K-160 to R-174; G-161 to G-175; S-162 to S-176; Y-163 to A-177; T-164 to L-178; F-165 to E-179; V-166 to E-180; P-167 to K-181; W-168 to E-182; L-169 to N-183; L-170 to K-184; S-171 to I-185; F-172 to L-186; K-173 to V-187; R-174 to K-188; G-175 to E-189; S-176 to T-190; A-177 to G-191; L-178 to Y-192; E-179 to F-193; E-180 to F-194; K-181 to I-195; E-182 to Y-196; N-183 to G-197; K-184 to Q-198; I-185 to V-199; L-186 to L-200; V-187 to Y-201; K-188 to T-202; E-189 to D-203; T-190 to K-204; G-191 to T-205; Y-192 to Y-206; F-193 to A-207; F-194 to M-208; I-195 to G-209; Y-196 to H-210; G-197 to L-211; Q-198 to I-212; V-199 to Q-213; L-200 to R-214; Y-201 to K-215; T-202 to K-216; D-203 to V-217; K-204 to H-218; T-205 to V-219; Y-206 to F-220; A-207 to G-221; M-208 to D-222; G-209 to E-223; H-210 to L-224; L-211 to S-225; I-212 to L-226; Q-213 to V-227; R-214 to T-228; K-215 to L-229; K-216 to F-230; V-217 to R-231; H-218 to C-232; V-219 to I-233; F-220 to Q-234; G-221 to N-235; D-222 to M-236; E-223 to P-237; L-224 to E-238; S-225 to T-239; L-226 to L-240; V-227 to P-241; T-228 to N-242; L-229 to N-243; F-230 to S-244; R-231 to C-245; C-232 to Y-246; I-233 to S-247; Q-234 to A-248; N-235 to G-249; M-236 to I-250; P-237 to A-251; E-238 to K-252; T-239 to L-253; L-240 to E-254; P-241 to E-255; N-242 to G-256; N-243 to D-257; S-244 to E-258; C-245 to L-259; Y-246 to Q-260; S-247 to L-261; A-248 to A-262; G-249 to I-263; I-250 to P-264;

A-251 to R-265; K-252 to E-266; L-253 to N-267; E-254 to A-268; E-255 to Q-269; G-256 to I-270; D-257 to S-271; E-258 to L-272; L-259 to D-273; Q-260 to G-274; L-261 to D-275; A-262 to V-276; I-263 to T-277; P-264 to F-278; R-265 to F-279; E-266 to G-280; N-267 to A-281; A-268 to L-282; Q-269 to K-283; I-270 to L-284; and S-271 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

**[0144]** In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to G-142;

S-129 to S-143; R-130 to Y-144; N-131 to T-145; K-132 to F-146; R-133 to V-147; A-134 to P-148; V-135 to W-149; Q-136 to L-150; G-137 to L-151; P-138 to S-152; E-139 to F-153; E-140 to K-154; T-141 to R-155; G-142 to G-156; S-143 to S-157; Y-144 to A-158; T-145 to L-159; F-146 to E-160; V-147 to E-161; P-148 to K-162; W-149 to E-163; L-150 to N-164; L-151 to K-165; S-152 to I-166; F-153 to L-167; K-154 to V-168; R-155 to K-169; G-156 to E-170; S-157 to T-171; A-158 to G-172; L-159 to Y-173; E-160 to F-174; E-161 to F-175; K-162 to I-176; E-163 to Y-177; N-164 to G-178; K-165 to Q-179; I-166 to V-180; L-167 to L-181; V-168 to Y-182; K-169 to T-183; E-170 to D-184; T-171 to K-185; G-172 to T-186; Y-173 to Y-187; F-174 to A-188; F-175 to M-189; I-176 to G-190; Y-177 to H-191; G-178 to L-192; Q-179 to I-193; V-180 to Q-194; L-181 to R-195; Y-182 to K-196; T-183 to K-197; D-184 to V-198; K-185 to H-199; T-186 to V-200; Y-187 to F-201; A-188 to G-202; M-189 to D-203; G-190 to E-204; H-191 to L-205; L-192 to S-206; I-193 to L-207; Q-194 to V-208; R-195 to T-209; K-196 to L-210; K-197 to F-211; V-198 to R-212; H-199 to C-213; V-200 to I-214; F-201 to Q-215; G-202 to N-216; D-203 to M-217; E-204 to P-218; L-205 to E-219; S-206 to T-220; L-207 to L-221; V-208 to P-222; T-209 to N-223; L-210 to N-224; F-211 to S-225; R-212 to C-226; C-213 to Y-227; I-214 to S-228; Q-215 to A-229; N-216 to G-230; M-217 to I-231; P-218 to A-232; E-219 to K-233; T-220 to L-234; L-221 to E-235; P-222 to E-236; N-223 to G-237; N-224 to D-238; S-225 to E-239; C-226 to L-240; Y-227 to Q-241; S-228 to L-242; A-229 to A-243; G-230 to I-244; I-231 to P-245; A-232 to R-246; K-233 to E-247; L-234 to N-248; E-235 to A-249; E-236 to Q-250; G-237 to I-251; D-238 to S-252; E-239 to L-253; L-240 to D-254; Q-241 to G-255; L-242 to D-256; A-243 to V-257; I-244 to T-258; P-245 to F-259; R-246 to F-260; E-247 to G-261; N-248 to A-262; A-249 to L-263; Q-250 to K-264; I-251 to L-265; and S-252 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0145]** In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to F-15; D-2 to C-16; E-3 to S-17; S-4 to E-18; A-5 to K-19; K-6 to G-20; T-7 to E-21; L-8 to D-22; P-9 to M-23; P-10 to K-24;



P-11 to V-25; C-12 to G-26; L-13 to Y-27; C-14 to D-28; F-15 to P-29; C-16 to I-30; S-17 to T-31; E-18 to P-32; K-19 to Q-33; G-20 to K-34; E-21 to E-35; D-22 to E-36; M-23 to G-37; K-24 to A-38; V-25 to W-39; G-26 to F-40; Y-27 to G-41; D-28 to I-42; P-29 to C-43; I-30 to R-44; T-31 to D-45; P-32 to G-46; Q-33 to R-47; K-34 to L-48; E-35 to L-49; E-36 to A-50; G-37 to A-51; A-38 to T-52; W-39 to L-53; F-40 to L-54; G-41 to L-55; I-42 to A-56; C-43 to L-57; R-44 to L-58; D-45 to S-59; G-46 to S-60; R-47 to S-61; L-48 to F-62; L-49 to T-63; A-50 to A-64; A-51 to M-65; T-52 to S-66; L-53 to L-67; L-54 to Y-68; L-55 to Q-69; A-56 to L-70; L-57 to A-71; L-58 to A-72; S-59 to L-73; S-60 to Q-74; S-61 to A-75; F-62 to D-76; T-63 to L-77; A-64 to M-78; M-65 to N-79; S-66 to L-80; L-67 to R-81; Y-68 to M-82; Q-69 to E-83; L-70 to L-84; A-71 to Q-85; A-72 to S-86; L-73 to Y-87; Q-74 to R-88; A-75 to G-89; D-76 to S-90; L-77 to A-91; M-78 to T-92; N-79 to P-93; L-80 to A-94; R-81 to A-95; M-82 to A-96; E-83 to G-97; L-84 to A-98; Q-85 to P-99; S-86 to E-100; Y-87 to L-101; R-88 to T-102; G-89 to A-103; S-90 to G-104; A-91 to V-105; T-92 to K-106; P-93 to L-107; A-94 to L-108; A-95 to T-109; A-96 to P-110; G-97 to A-111; A-98 to A-112; P-99 to P-113; E-100 to R-114; L-101 to P-115; T-102 to H-116; A-103 to N-117; G-104 to S-118; V-105 to S-119; K-106 to R-120; L-107 to G-121; L-108 to H-122; T-109 to R-123; P-110 to N-124; A-111 to R-125; A-112 to R-126; P-113 to A-127; R-114 to F-128; P-115 to Q-129; H-116 to G-130; N-117 to P-131; S-118 to E-132; S-119 to E-133; R-120 to T-134; G-121 to E-135; H-122 to Q-136; R-123 to D-137; N-124 to V-138; R-125 to D-139; R-126 to L-140; A-127 to S-141; F-128 to A-142; Q-129 to P-143; G-130 to P-144; P-131 to A-145; E-132 to P-146; E-133 to C-147; T-134 to L-148; E-135 to P-149; Q-136 to G-150; D-137 to C-151; V-138 to R-152; D-139 to H-153; L-140 to S-154; S-141 to Q-155; A-142 to H-156; P-143 to D-157; P-144 to D-158; A-145 to N-159; P-146 to G-160; C-147 to M-161; L-148 to N-162; P-149 to L-163; G-150 to R-164; C-151 to N-165; R-152 to I-166; H-153 to I-167; S-154 to Q-168; Q-155 to D-169; H-156 to C-170; D-157 to L-171; D-158 to Q-172; N-159 to L-173; G-160 to I-174; M-161 to A-175; N-162 to D-176; L-163 to S-177; R-164 to D-178; N-165 to T-179; I-166 to P-180; I-167 to A-181; Q-168 to L-182; D-169 to E-183; C-170 to E-184; L-171 to K-185; Q-172 to E-186; L-173 to N-187; I-174 to K-188; A-175 to I-189; D-176 to V-190; S-177 to V-191; D-178 to R-192; T-179 to Q-193; P-180 to T-194; A-181 to G-195; L-182 to Y-196; E-183 to F-197; E-184 to F-198; K-185 to I-199; E-186 to Y-200; N-187 to S-201; K-188 to Q-202; I-189 to V-203; V-190 to L-204; V-191 to Y-205; R-192 to T-

206; Q-193 to D-207; T-194 to P-208; G-195 to I-209; Y-196 to F-210; F-197 to A-211; F-198 to M-212; I-199 to G-213; Y-200 to H-214; S-201 to V-215; Q-202 to I-216; V-203 to Q-217; L-204 to R-218; Y-205 to K-219; T-206 to K-220; D-207 to V-221; P-208 to H-222; I-209 to V-223; F-210 to F-224; A-211 to G-225; M-212 to D-226; G-213 to E-227; H-214 to L-228; V-215 to S-229; I-216 to L-230; Q-217 to V-231; R-218 to T-232; K-219 to L-233; K-220 to F-234; V-221 to R-235; H-222 to C-236; V-223 to I-237; F-224 to Q-238; G-225 to N-239; D-226 to M-240; E-227 to P-241; L-228 to K-242; S-229 to T-243; L-230 to L-244; V-231 to P-245; T-232 to N-246; L-233 to N-247; F-234 to S-248; R-235 to C-249; C-236 to Y-250; I-237 to S-251; Q-238 to A-252; N-239 to G-253; M-240 to I-254; P-241 to A-255; K-242 to R-256; T-243 to L-257; L-244 to E-258; P-245 to E-259; N-246 to G-260; N-247 to D-261; S-248 to E-262; C-249 to I-263; Y-250 to Q-264; S-251 to L-265; A-252 to A-266; G-253 to I-267; I-254 to P-268; A-255 to R-269; R-256 to E-270; L-257 to N-271; E-258 to A-272; E-259 to Q-273; G-260 to I-274; D-261 to S-275; E-262 to R-276; I-263 to N-277; Q-264 to G-278; L-265 to D-279; A-266 to D-280; I-267 to T-281; P-268 to F-282; R-269 to F-283; E-270 to G-284; N-271 to A-285; A-272 to L-286; Q-273 to K-287; I-274 to L-288; and S-275 to L-289 of SEQ ID NO:38. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

**[0146]** It will be recognized by one of ordinary skill in the art that some amino acid sequences of the BLyS polypeptides can be varied without significant effect of the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine activity.

**[0147]** Thus, the invention further includes antibodies that bind variations of BLyS polypeptides which show BLyS polypeptide functional activity (e.g., biological activity) or which include regions of BLyS polypeptide such as the polypeptide fragments described herein. Such mutants include deletions, insertions, inversions, repeats, and type substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., "Deciphering the Message in Protein

Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main approaches for studying the tolerance of an amino acid sequence to change. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

[0148] As the authors state, these studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described in Bowie, J. U. *et al.*, *supra*, and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

[0149] Thus, antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3228, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence.

[0150] Antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3229, or that encoded by the deposited cDNA

plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as, a soluble biologically active fragment of another TNF ligand family member (e.g., CD40 Ligand), an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

**[0151]** Thus, the antibodies of the invention may bind BLYS polypeptides that include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 13).

**[0152]** TABLE 13. Conservative Amino Acid Substitutions.

<b>[0153]</b>	Aromatic	<b>[0159]</b>	Phenylalanine
		<b>[0160]</b>	Tryptophan
		<b>[0161]</b>	Tyrosine
<b>[0154]</b>	Hydrophobic	<b>[0162]</b>	Leucine
		<b>[0163]</b>	Isoleucine
		<b>[0164]</b>	Valine
<b>[0155]</b>	Polar	<b>[0165]</b>	Glutamine
		<b>[0166]</b>	Asparagine
<b>[0156]</b>	Basic	<b>[0167]</b>	Arginine
		<b>[0168]</b>	Lysine
		<b>[0169]</b>	Histidine
<b>[0157]</b>	Acidic	<b>[0170]</b>	Aspartic Acid
		<b>[0171]</b>	Glutamic Acid

<p><b>[0158]</b>            Small</p>	<p><b>[0172]</b>            Alanine  <b>[0173]</b>            Serine  <b>[0174]</b>            Threonine  <b>[0175]</b>            Methionine  <b>[0176]</b>            Glycine</p>
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**[0177]**            In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLyS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLyS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

**[0178]**            For example, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with

A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A,

I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M; T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced with E; L147 replaced with A, G, I, S, T, M, or V; Q148 replaced with N; L149 replaced with A, G, I, S, T, M, or V; I150 replaced with A, G, L, S, T, M, or V; A151 replaced with G, I, L, S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154 replaced with D; T155 replaced with A, G, I, L, S, M, or V; T157 replaced with A, G, I, L, S, M, or V; I158 replaced with A, G, L, S, T, M, or V; Q159 replaced with N; K160 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A, G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, S, T, M, or V; S171 replaced with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184 replaced with H, or R; I185 replaced with A, G, L, S, T, M, or V; L186 replaced with A, G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194 replaced with W, or Y; I195 replaced with A, G, L, S, T, M, or V; Y196 replaced with F, or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaced with E; K204 replaced with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W; A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V;

G209 replaced with A, I, L, S, T, M, or V; H210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; L212 replaced with A, G, L, S, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H, or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaced with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaced with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaced with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, L, S, M, or V; L229 replaced with A, G, I, S, T, M, or V; F230 replaced with W, or Y; R231 replaced with H, or K; L233 replaced with A, G, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaced with A, I, L, S, T, M, or V; D257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; I263 replaced with A, G, L, S, T, M, or V; R265 replaced with H, or K; E266 replaced with D; N267 replaced with Q; A268 replaced with G, I, L, S, T, M, or V; Q269 replaced with N; I270 replaced with A, G, L, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, I, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or L285 replaced with A, G, I, S, T, M, or V.

[0179] In another embodiment, site directed changes at the amino acid level of BLYs can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLYs amino acid sequences containing



conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S,

T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; G142 replaced with A, I, L, S, T, M, or V; S143 replaced with A, G, I, L, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, or M; W149 replaced with F, or Y; L150 replaced with A, G, I, S, T, M, or V; L151 replaced with A, G, I, S, T, M, or V; S152 replaced with A, G, I, L, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, L, S, T, M, or V; L167 replaced with A, G, I, S, T, M, or V; V168 replaced with A, G, I, L, S, T, or M; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L, S, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174

replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, I, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, or M; L181 replaced with A, G, I, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, S, T, M, or V; I193 replaced with A, G, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, or M; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, or M; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, S, T, M, or V; S206 replaced with A, G, I, L, T, M, or V; L207 replaced with A, G, I, S, T, M, or V; V208 replaced with A, G, I, L, S, T, or M; T209 replaced with A, G, I, L, S, M, or V; L210 replaced with A, G, I, S, T, M, or V; F211 replaced with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, M, or V; L221 replaced with A, G, I, S, T, M, or V; N223 replaced with Q; N224 replaced with Q; S225 replaced with A, G, I, L, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, T, M, or V; A229 replaced with G, I, L, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; I231 replaced with A, G, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaced with H, or R; L234 replaced with A, G, I, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, S, T, M, or V; Q241 replaced with N; L242 replaced with A, G, I, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; I244 replaced with A, G, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, L, S, T, M, or V; S252 replaced with A, G, I, L, T, M, or V; L253 replaced with A, G, I, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, or M; T258 replaced with A, G, I, L, S, M, or V; F259 replaced with W, or Y; F260 replaced

with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, S, T, M, or V; K264 replaced with H, or R; L265 replaced with A, G, I, S, T, M, or V; and/or L266 replaced with A, G, I, S, T, M, or V.

**[0180]** In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

**[0181]** Amino acids in the BLyS polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the BLyS polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the BLyS polypeptides that are essential for function and inhibit BLyS polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the BLyS polypeptides that are essential for function and enhance BLyS polypeptide function.

**[0182]** Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic (Pinckard *et al.*, *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins *et al.*, *Diabetes* 36: 838-845 (1987); Cleland *et al.*, *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993).

**[0183]** In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the BLyS protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L,

S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or

C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with

D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D,

E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q144 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D145 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C146 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L149 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D152 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S153 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E154 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T155 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P156 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q159 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K160 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G161 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S162 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y163 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T164 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F165 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P167 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W168 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L169 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L170 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F172 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K173 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R174 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G175 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A177 replaced with D, E, H, K, R, N, Q, F, W,



Y, P, or C; L178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E179 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E180 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K181 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E182 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N183 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K184 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I185 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V187 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K188 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E189 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G191 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y192 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F193 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F194 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I195 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y196 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G197 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q198 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V199 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K204 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y206 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H210 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L211 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R214 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K215 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K216 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H218 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V219 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F220 replaced with D, E, H, K, R, N, Q, A, G, I, L, S,

T, M, V, P, or C; G221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D222 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E223 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L224 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L226 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V227 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F230 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R231 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C232 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I233 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q234 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N235 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M236 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P237 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T239 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N242 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N243 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y246 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S247 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A248 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K252 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E255 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G256 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D257 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E258 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L259 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q260 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I263 replaced with D, E, H, K, R, N,

Q, F, W, Y, P, or C; P264 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R265 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E266 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N267 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A268 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q269 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I270 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S271 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L272 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D273 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G274 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D275 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V276 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T277 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F278 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F279 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G280 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A281 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K283 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L284 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L285 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

**[0184]** In an additional embodiment, antibodies of the present invention bind BLyS polypeptides comprising, or alternatively consisting of, a BLyS amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

**[0185]** In another embodiment of the invention, antibodies of the present invention bind BLyS polypeptides with non-conservative substitutions of the sequence provided in SEQ ID NO:3229 including: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I,

L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N,

[illegible]

E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

S143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y144 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T145 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F146 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W149 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S152 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F153 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K154 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L155 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G156 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L159 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E160 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E161 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K162 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E163 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N164 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K165 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L167 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V168 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K169 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E170 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G172 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y173 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F174 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F175 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y177 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q179 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V180 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L181 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y182 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T183 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D184 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K185 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T186





A229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G230 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I231 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K233 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L234 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E235 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E236 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E239 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L242 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R246 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E247 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N248 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q250 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S252 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G255 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D256 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V257 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T258 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F259 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F260 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K264 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L265 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L266 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

**[0186]** In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a non-conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing non-conservative substitution mutations of the polypeptide of any one of SEQ

ID NOS:3230-3237.

**[0187]** In an additional embodiment, antibodies of the present invention bind BLyS polypeptides comprising, or alternatively consisting of, a BLyS amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

**[0188]** Replacement of amino acids can also change the selectivity of the binding of a ligand to cell surface receptors. For example, Ostade *et al.*, *Nature* 361:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Since BLyS is a member of the TNF polypeptide family, mutations similar to those in TNF-alpha are likely to have similar effects in BLyS polypeptides.

**[0189]** Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992) and de Vos *et al. Science* 255:306-312 (1992)).

**[0190]** Since BLyS is a member of the TNF-related protein family, mutations may be made in sequences encoding amino acids in the TNF conserved domain, e.g., in positions Gly-191 through Leu-284 of SEQ ID NO:3228 or in positions Gly-172 through Leu-265 of SEQ ID NO:3229, may modulate rather than completely eliminate functional activities (e.g., biological activities) of BLyS polypeptides or fragments or variants thereof. Accordingly, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain. In preferred embodiments, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain and act as antagonists of BLyS. In other preferred embodiments, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain and act as agonists of BLyS.

**[0191]** Recombinant DNA technology known to those skilled in the art (see, for instance, DNA shuffling *supra*) can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than

the corresponding natural polypeptide, at least under certain purification and storage conditions.

**[0192]** Thus, the invention also encompasses antibodies that bind BLYS derivatives and analogs that have one or more amino acid residues deleted, added, or substituted to generate BLYS polypeptides, e.g., that are better suited for expression, scale up, etc., in the host cells. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the BLYS polypeptides of the invention, and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the BLYS at the modified tripeptide sequence (see, e.g., Miyajimo et al., EMBO J 5(6):1193-1197). By way of non-limiting example, mutation of the serine at position 244 to alanine either singly or in combination with mutation of the asparagine at position 242 to glutamine abolishes glycosylation of the mature soluble form of BLYS (e.g., amino acids 134-285 of SEQ ID NO:3228) when expressed in the yeast *Pichia pastoris*. A mutant BLYS polypeptide in which only the asparagine at position 242 is mutated to glutamine, is still glycosylated when expressed in *Pichia pastoris*. In this mutant, the glycosylation event may be due to the activation or unmasking of an O-linked glycosylation site at serine 244. Similar mutations affecting glycosylation could also be made in the BLYS polypeptide of SEQ ID NO:3229, i.e., asparagine-223 to glutamine and/or serine-224 to alanine of SEQ ID NO:3229. Additionally, one or more of the amino acid residues of the polypeptides of the invention (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins. One possible result of such a mutation is that BLYS polypeptide of the invention is not cleaved and released from the cell surface. Accordingly, antibodies of the invention may bind BLYS derivatives and analogs that have one or more amino acid residues deleted, added, or substituted. In other embodiments, antibodies of the invention may bind BLYS derivatives, variants or analogs that are unable to be cleaved from the cell surface.

**[0193]** In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Lys-132 and/or Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, to prevent or diminish release of the soluble form of BLyS from cells expressing BLyS. In a more specific embodiment, antibodies of the invention bind BLyS polypeptides in which Lys-132 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to Ala-132. In another, nonexclusive specific embodiment, antibodies of the invention bind BLyS polypeptides in which Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to Ala-133. These mutated proteins, and/or have uses such as, for example, in ex vivo therapy or gene therapy, to engineer cells expressing a BLyS polypeptide that is retained on the surface of the engineered cells.

**[0194]** In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-146 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-146 is replaced with a serine amino acid residue.

**[0195]** In another specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-232 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-232 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

**[0196]** In yet another specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-245 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-245 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

**[0197]** The polypeptides of the present invention are preferably provided in an

isolated form, and preferably are substantially purified. A recombinantly produced version of the BLyS polypeptides can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988).

**[0198]** The antibodies of the present invention bind BLyS polypeptides including the complete polypeptide encoded by the deposited cDNA (ATCC Deposit No. 97768) including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA, the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3228, the mature soluble polypeptide of SEQ ID NO:3228, e.g., amino acids 134-285 of SEQ ID NO:3228, the extracellular domain of SEQ ID NO:3228, amino acid residues 73-285 of SEQ ID NO:3228 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0199]** The antibodies of the present invention bind BLyS polypeptides including the complete polypeptide encoded by the deposited cDNA including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 203518), the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3229, the mature soluble of SEQ ID NO:3229, e.g., amino acid residues 134-266 of SEQ ID NO:3229, the extracellular domain of SEQ ID NO:3229, e.g., amino acid residues 73-266 of SEQ ID NO:3229 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0200]** Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 97768) or to the polypeptide of SEQ

ID NO:3228, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

**[0201]** Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 203518) or to the polypeptide of SEQ ID NO:3229, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0202]** By "% similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2:482-489, 1981) to find the best segment of similarity between two sequences.

**[0203]** By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a BLyS polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the BLyS polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

**[0204]** As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of SEQ ID NO:3228, the amino acid sequence encoded by the deposited cDNA

clone HNEDU15 (ATCC Accession No. 97768), or fragments thereof, or, for instance, to the amino acid sequence of SEQ ID NO:3229, the amino acid sequence encoded by the deposited cDNA clone HDPMC52 (ATCC Accession No. 203518), or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

**[0205]** In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is

what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

**[0206]** Antibodies that Immunospecifically bind BLyS Polypeptides

**[0207]** The present invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS polypeptides, which antibodies comprise, or alternatively consist of, all or a portion of a heavy and/or light chain variable domain of the scFvs referred to in Table 1.

**[0208]** The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can



be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

**[0209]** The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLYS or BLYS receptor expression or inappropriate BLYS or BLYS receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLYS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

**[0210]** Anti-BLYS Antibodies

**[0211]** The antibodies of the present invention were discovered, in part, using phage display technology. Single chain antibody molecules ("scFvs") displayed on the surface of phage particles were screened to identify those scFvs that immunospecifically bind to BLYS, including the membrane-bound form and soluble form of BLYS. The present invention encompasses the scFvs and portions thereof that were identified to immunospecifically bind to BLYS, including scFvs that immunospecifically bind to the soluble form of BLYS, scFvs that immunospecifically bind to the membrane-bound form of BLYS, and scFvs that immunospecifically bind to both the soluble form and membrane-bound form of BLYS. In particular, the present invention encompasses scFvs comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NOS: 1 - 2128, as referred to in Table 1. Preferably, the scFvs of the present invention comprise, or alternatively consist of, the amino acid sequence of SEQ ID NOS: 1 - 46, 321 - 329, 834 -

872, 1563 - 1595, or 1881 - 1908. The scFvs include scFvs that bind to soluble BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1880), scFvs that bind to the membrane-bound form of BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128), and scFvs that bind to both the soluble form and the membrane-bound form of BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562). Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

**[0212]** In one embodiment of the present invention, scFvs that immunospecifically bind to BLyS comprise a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1 and/or any one of the VL domains referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1 and/or any one, two, three, or more of the VL CDRs referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the scFvs referred to in Table 1 that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

**[0213]** (Table 1 can be found at the end of the specification just prior to the claims.)

**[0214]** In another embodiment of the present invention, an scFv that immunospecifically binds to a soluble form of BLyS, comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 – 1880 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1570 - 1595. In an even more preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 - 1569.

**[0215]** In another embodiment of the present invention, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 2128 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1886 - 1908. In an even more preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 1885.

**[0216]** In another embodiment of the present invention, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1 - 1562 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:834 - 872. In another preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, any one of the amino acids sequences of SEQ ID NOS:1 – 46 or 321 - 329. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to the soluble form of BLyS and/or the membrane-bound form of BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

**[0217]** In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1563 –

1880 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in contained SEQ ID NOS:1563 - 1880, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLYS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLYS, preferably the soluble form of BLYS, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

**[0218]** In another embodiment of the present invention, scFvs that

immunospecifically bind to the membrane-bound form of BLyS comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS, preferably the membrane-bound form of BLyS, are

also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0219] In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form and membrane-bound form of BLYS, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLYS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of BLYS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form and membrane-bound form of BLYS comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of BLYS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLYS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble and membrane-bound forms of BLYS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS:1 - 1562, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLYS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention

that immunospecifically bind to the soluble and membrane-bound forms of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs or molecules, that immunospecifically bind to BLyS, preferably the soluble and membrane-bound forms of BLyS, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

**[0220]** The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1, such scFvs may routinely be “converted” to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 20, *infra*.

**[0221]** In one embodiment, the invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one of the VH domains contained in the sequences referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide, or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that immunospecifically bind to BLyS or a BLyS fragment are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

**[0222]** In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR referred to in Table 1. In

particular, the invention provides antibodies that immunospecifically bind BLYS, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind BLYS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind BLYS, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind BLYS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1; a VH CDR2 contained in SEQ ID NOS: SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908; and/or a VH CDR3 contained in SEQ ID NOS: SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VH CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to BLYS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

**[0223]** The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide, or polypeptide fragment of BLYS. In particular, the invention provides antibodies wherein said antibodies comprise, or alternatively consist of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of BLYS, wherein said antibodies comprise, or alternatively consist of, a VL CDR having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to BLYS are also encompassed by the



invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

**[0224]** In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind BLyS, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind BLyS comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In a preferred embodiment, antibodies comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS: in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind BLyS comprise, or alternatively consist of: a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1; a VL CDR2 SEQ ID NOS :834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1; and a VL CDR3 contained SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VL CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

**[0225]** The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VH domain of one of the scFvs referred to in Table 1 combined with a VL domain of one of the scFvs referred to in Table 1, or other VL domain. The present invention further provides antibodies (including

molecules comprise, or alternatively consist of, antibody fragments or variants thereof that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VL domain of one of the scFvs referred to in Table 1 combined with a VH domain of one of the scFvs referred to in Table 1, or other VH domain. In a preferred embodiment, antibodies that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1 and a VL domain contained in contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1. In a further preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a VH and a VL domain from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

**[0226]** The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as referred to in Table 1. In particular, the invention provides for antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VH CDRs and VL CDRs referred to in Table 1. In a preferred embodiment, one or more of these combinations are from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

**[0227]** In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1, 2, or 3) and VL CDRY (where Y= 1, 2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLyS, from scFvs that bind membrane-bound BLyS, or from scFvs that bind both soluble and membrane-bound BLyS. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

**[0228]** The term “antibody,” as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term “antibody” encompasses not only whole antibody molecules, but also antibody fragments, as well as variants (including derivatives) of antibodies and antibody fragments. Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, single chain Fvs (scFvs), Fab fragments, F(ab')<sub>2</sub> fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or subclass of immunoglobulin molecule. The antibodies of the present invention also include molecules comprising, or alternatively consisting of, a polypeptide having an amino acid sequence of a portion of an amino acid sequence contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908. Preferably, an antibody of the invention comprises, or alternatively consists of, a polypeptide having an amino acid sequence of a VH domain, VH CDR, VL domain, or VL CDR of any one those contained in the sequences referred to in Table 1. Antibodies of the invention also include molecules comprising, or alternatively consisting of, fragments or variants of the above antibodies that immunospecifically bind BLyS.

**[0229]** Most preferably the antibodies of the present invention are whole antibodies or antibody fragments that immunospecifically bind human BLyS. Antibody fragments of the invention that immunospecifically bind human BLyS include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd fragments, single-chain Fvs (scFv), single-chain

antibodies, disulfide-linked Fvs (sdFvs), fragments comprising, or alternatively consisting of, either a VL or VH domain, and epitope binding fragments of any of the above.

[0230] BLYS-binding antibody fragments, including single-chain antibodies, may comprise, or alternatively consist of, the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. In a preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a polypeptide that immunospecifically binds to BLYS, said polypeptides comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs referred to in Table 1, preferably a polypeptide having an amino acid sequence of a VH CDR3 and/or a VL CDR3 of contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1. Most preferably, antibodies of the invention comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs from the same scFv, as referred to in Table 1. The antibodies of the invention may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenomice or other organisms that have been genetically engineered to produce human antibodies. For a detailed discussion of a few of the technologies for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598; and Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995), which are incorporated by reference herein in their entirety. Human antibodies or "humanized" chimeric monoclonal antibodies can be produced using techniques described herein or otherwise known in the art. For example, methods for producing chimeric antibodies are known in the art. See, for review the following references which are hereby incorporated in their entirety: Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., *Nature* 312:643 (1984);

Neuberger *et al.*, *Nature* 314:268 (1985). In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

**[0231]** The antibodies of the present invention may be monovalent, bivalent, trivalent or multivalent. For example, monovalent scFvs can be multimerized either chemically or by association with another protein or substance. An scFv that is fused to a hexahistidine tag or a Flag tag can be multimerized using Ni-NTA agarose (Qiagen) or using anti-Flag antibodies (Stratagene, Inc.).

**[0232]** The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a BLyS polypeptide, or fragment thereof, or may be specific for both a BLyS polypeptide, or fragment thereof, and a heterologous epitope, such as a heterologous polypeptide or solid support material. See, *e.g.*, PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, *et al.*, *J. Immunol.* 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, *J. Immunol.* 148:1547-1553 (1992).

**[0233]** The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may bind immunospecifically to murine BLyS (*e.g.*, a polypeptide having the amino acid sequence of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (*e.g.*, the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes), preferably the antibodies of the invention bind immunospecifically to human BLyS. Preferably, the antibodies of the invention bind immunospecifically to human and monkey BLyS. Also preferably, the antibodies of the invention bind immunospecifically to human BLyS and murine BLyS. More preferably, antibodies of the invention, bind immunospecifically and with higher affinity to human BLyS than to murine BLyS.

**[0234]** Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, antibodies of the present invention cross react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6):1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under hybridization conditions (as described herein).

**[0235]** In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), immunospecifically bind to BLyS and do not cross-react with any other antigens. In more preferred embodiments, the antibodies of the invention immunospecifically bind to BLyS and do not cross-react with TRAIL, APRIL, Endokine-alpha, TNF-alpha, TNF-beta, Fas-L or LIGHT.

**[0236]** The present invention also provides for a nucleic acid molecule, generally

**[0237]** isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In one embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the

VH domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1 having an amino acid sequence of any one of the VH CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR2 having an amino acid sequence of any one of the VH CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR3 having an amino acid sequence of any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding antibodies that immunospecifically bind BLYS and comprise, or alternatively consist of, fragments or variants of the VH domains and/or VH CDRs are also encompassed by the invention.

**[0238]** In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR1 having amino acid sequence of any one of the VL CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR2 having an amino acid sequence of any one of the VL CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR3 having an amino acid sequence of any one of the VL CDR3s referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind BLYS and comprise, or alternatively consist of, fragments or variants of the VL domains and/or VLCDR(s) are also encompassed by the invention.

**[0239]** In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1 and a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an

nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0628]** In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0629]** In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, wherein the antibody or fragment thereof immunospecifically binds the membrane-bound form of BLyS. The present invention also



encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0630]** In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, wherein said antibody or fragment thereof immunospecifically binds the soluble form of BLYS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0631]** In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLYS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the

present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0632]** In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and in which said VL domain and said VH domain are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0633]** In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VHCDR3 from an scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227, wherein said antibody or fragment thereof immunospecifically binds BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells,

comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

**[0634]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

**[0635]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

**[0636]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

**[0637]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

**[0638]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence

that hybridizes under stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

**[0639]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

**[0640]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

**[0641]** In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLYS, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

**[0642]** In specific embodiments, the present invention provides a method for detecting of aberrant expression of BLYS, comprising:

**[0643]** assaying the level of BLYS expression in cells or a tissue sample of an individual using one or more antibodies or fragments or variants thereof that immunospecifically bind BLYS; and

**[0644]** comparing the level of BLYS assayed in the cells or a tissue sample with a standard level of BLYS or a level of BLYS in cells or a tissue sample from an individual without aberrant BLYS expression, wherein an increase or decrease in the assayed level of BLYS or level in cells or a tissue sample from an individual without aberrant BLYS expression compared to the standard level of BLYS is indicative of aberrant expression.

**[0645]** In specific embodiments, the present invention provides a method for diagnosing a disease or disorder associated with aberrant BLYS expression or activity, comprising:

**[0646]** administering to a subject an effective amount of a labeled antibody or

fragment thereof that immunospecifically binds to BLyS;

[0647] waiting for a time interval following the administering for permitting the labeled antibody or fragment thereof to preferentially concentrate at sites in the subject where BLyS is expressed;

[0648] determining background level; and

[0649] detecting the labeled antibody or fragment thereof in the subject, such that detection of labeled antibody or fragment thereof above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of BLyS.

[0650] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0651] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0652] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

[0653] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent.

[0654] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase.

[0655] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin.

[0656] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{90}\text{Y}$  or  $^{99}\text{Tc}$ .

[0657] In specific embodiments, the antibody or fragment thereof utilized in the

two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is luciferase, luciferin or aequorin.

**[0658]** A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier.

**[0659]** A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier.

**[0660]** A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier.

**[0661]** A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier.

**[0662]** A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

**[0663]** A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an

animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

**[0664]** A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

**[0665]** A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition of comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

**[0666]** This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

## EXAMPLES

### Abbreviations

0.2 M Tris-HCl, 0.5 mM EDTA, 0.5 M sucrose (TES)

1-ethyl-3-[3-dimethylaminopropyl]carbo diimide hydrochloride (EDC)

2TY supplemented with 100µg/ml ampicillin and 2% glucose (2TYAG)

2TY supplemented with 100µg/ml ampicillin and 50µg/ml kanamycin (2TYAK)

3,3',5,5'-Tetramethyl Benzidine (TMB)

50% inhibitory concentration (IC<sub>50</sub>)

6xPBS containing 18% Marvel blocking solution (6xMPBS)

Absorbance (A)

Bovine serum albumin (BSA)

Enzyme linked immunosorbent assay (ELISA)

Foetal calf serum (FCS)

Heavy chain variable (V<sub>H</sub>)

Hepes buffered saline (HBS)

Horseradish peroxidase (HRP)

Immobilised Metal Affinity Chromatography (IMAC)

Isopropyl β-D-thiogalactopyranoside (IPTG)

Light chain variable (V<sub>L</sub>)

Multiplicity of infection (MOI)

N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] (Hepes)

Nanomolar (nM)

N-Hydroxysuccinimide (NHS)

PBS containing 3% Marvel (MPBS)

Phosphate Buffered Saline (PBS)

Phosphate Buffered Saline + 0.1% (v/v) Tween 20 (PBST)

Picomolar (pM)

Single chain fragment variable (scFv)

Tumour Necrosis Factor-alpha (TNF-α)

Tumour Necrosis Factor-beta (TNF-β)

TNF-related apoptosis inducing ligand (TRAIL)

### Definitions:



**[0667]** In the following section “immobilized BLyS” refers to a soluble form of BLyS or biotinylated BLyS coated on a plastic assay plate (e.g., a 96 well plate), but does not refer to histidine tagged BLyS coated on a plastic assay plate.; “biotinylated BLyS” is a soluble form of BLyS except when used to coat an ELISA plate, in which case it would be “immobilized BLyS.” Membrane bound forms of BLyS include, but are not limited to, U937 and P388 plasma membranes.

#### Example 1: Antibodies Immunospecifically Binding to Soluble And Membrane-Bound BLyS

**[0668]** A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble and membrane-bound forms of BLyS. Phage displaying scFvs that bound to immobilized BLyS were identified after panning on immobilized BLyS and assessment by ELISA for binding to immobilized BLyS. The BLyS that was immobilized on plates for these assays was purified from supernatants of Sf9 cells infected with a baculovirus expression construct as described in Moore et al., Science 285:260-263 which is hereby incorporated by reference in its entirety. Each of the identified scFvs were then sequenced. Certain sequences were isolated multiple times, thus a panel (panel 1) containing one member of each unique sequences was generated and further characterized for their ability to immunospecifically bind to the soluble and membrane-bound forms of BLyS.

**[0669]** The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V<sub>H</sub> and V<sub>L</sub> segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, [www.mrc-cpe.cam.ac.uk](http://www.mrc-cpe.cam.ac.uk)) and the closest germline identified.

#### Example 2: Specificity of scFvs for BLyS and Membrane-Bound BLyS

**[0670]** The specificity of each of the scFvs for both BLyS and membrane-bound BLyS was determined by phage ELISA. BLyS was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937.

### Maintenance of U937 Cells

**[0671]** U937 cells are a human monocyte-like, histiocytic lymphoma cell line known to express BLyS on their plasma membranes. They were maintained in RPMI-1640 supplemented with 4mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells were thawed from frozen stock and are either used for plasma membrane preparation, or split 1:5, after 2 days in culture when the cell density reaches  $1 \times 10^6$ /ml.

### Preparation of U937 Plasma Membranes

**[0672]** To prepare plasma membranes,  $1 \times 10^9$  U937 cells were harvested from their culture medium by centrifugation at 1000 rpm at 4°C for 5 minutes in a benchtop centrifuge. The cells were resuspended in 40 ml 12 mM Tris, pH 7.5, 250 mM sucrose and placed on ice. The cells are then lysed using a hand-held electric homogenizer (Labortechnik IKA Ultra-Turrax) for four, one minute, bursts. To check that cell lysis had occurred, 10 µl cell lysate was added to 10 µl Trypan blue and the cell lysate was examined under a microscope. After confirming lysis, the homogenate was centrifuged at 270 x g, for 10 minutes at 4°C to pellet the nuclear fraction and the supernatant was retained. The supernatant was centrifuged at 8000 x g, 10 mins, 4°C, to pellet the mitochondrial and lysosomal fractions and the supernatant was retained. The supernatant was then centrifuged at 100000 x g, 60 mins, 4°C to pellet the plasma membrane enriched fraction. The supernatant was discarded and the plasma membrane pellet was resuspended in 1 ml PBS and stored at -70°C. The protein concentration of the plasma membrane fraction was determined using a protein quantification kit (Biorad). Typical yields were between 5 and 10 mg of plasma membranes.

### Phage ELISA

**[0673]** To determine the specificity of each of the unique scFvs, a phage ELISA was performed for each scFv against human BLyS, U937 plasma membranes, TNFα (R&D Systems, Minneapolis, MN), BSA and uncoated well. Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 µl 2TYAG medium per well. Plates were incubated at 37°C for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10

and the plates were incubated for a further 1 hour at 37°C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 µl 2TYAK and incubated at 30°C overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 µl phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Twenty µl of 6xMPBS was added to each well, and incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

**[0674]** Flexible 96-well plates (Falcon) were coated overnight at 4°C with human BLyS (1 µg/ml) in PBS, U937 plasma membranes (10 µg/ml) in PBS, TNFα (1 µg/ml) in PBS, BSA (1 µg/ml) in PBS, or PBS. After coating, the solutions were removed from the wells, and the plates were blocked for 1 hour at room temperature in MPBS. The plates were washed 3 times with PBS and then 50 µl of pre-blocked phage was added to each well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 µl of an anti-gene VIII-HRP conjugate (Pharmacia) at a 1 to 5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 µl of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1/50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty µl of TMB substrate was then added to each well, and incubated at room temperature for 30 minutes or until colour development. The reaction was stopped by the addition of 25 µl of 0.5 M H<sub>2</sub>SO<sub>4</sub>. The signal generated was measured by reading the absorbance at 450nm (A<sub>450</sub>) using a microtiter plate reader (Bio-Rad 3550).

**[0675]** The results for 3 clones (I006E07, I008D05 and I016F04) are shown in Figure 1. All 3 scFvs recognize immobilized BLyS and U937 plasma membranes but do not recognize TNFα, BSA or an uncoated well (PBS only). These results indicate that these scFvs specifically recognize immobilized BLyS and membrane-bound BLyS.

### Example 3: Inhibition in an *In Vitro* Receptor Binding Assay by Phage ScFvs

**[0676]** All of the unique phage scFvs in panel 1 were assessed for their ability to inhibit soluble BLyS binding to its cognate receptor on IM9 cells.

### Biotinylation of BLyS

**[0677]** One hundred µg of either human or mouse BLyS was dialysed overnight at 4° C against 50 mM sodium bicarbonate (sodium hydrogen carbonate) pH8.5 using a slide-a-lyzer cassette (Pierce). The next day, NHS-biotin (Pierce) was dissolved in DMSO to 13.3 mg/ml. This was then added to the BLyS at a molar ratio of 20:1 biotin:BLyS, mixed and incubated on ice for 2 hours. The biotinylated BLyS was then dialysed back into sterile PBS (Sigma) using a slide-a-lyzer cassette overnight at 4°C. The biological activity of the biotinylated BLyS was confirmed using the receptor binding inhibition assay (see below).

### Maintenance of IM9 cells

**[0678]** IM9 cells are a human B lymphocyte cell line. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells are thawed from frozen stock and can be used in assays after 5 days in culture when they reach a density of  $4 - 8 \times 10^5$  /ml.

### Receptor binding inhibition assay

**[0679]** Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 µl 2TYAG medium per well. Plates were incubated at 37° C for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37°C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 µl 2TYAK and incubated at 30°C overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 µl phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Phage were diluted 1 in 2 in MPBS prior to use.

**[0680]** Flat-bottomed 96-well plates (Costar) were coated with 100 µl per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4° C overnight. One hundred µl of IM9 cells (at  $10^6$ /ml in RPMI-1640 culture medium) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The

media was carefully aspirated and 200  $\mu$ l of MPBS added to each well. The plates were then allowed to block for 1 hour at room temperature.

**[0681]** To a separate 96-well plate 10  $\mu$ l of biotinylated BLyS (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Fifty-five  $\mu$ l of each appropriate phage supernatant was added to each well and the final volume in each well was 65  $\mu$ l. Plates were then incubated at room temperature for 30 minutes.

**[0682]** The IM9 coated plates were washed twice in PBS, tapped dry and immediately 50  $\mu$ l of the phage/biotinylated-BLyS mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50  $\mu$ l of streptavidin-Delfia (Wallac) was added to each well at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100  $\mu$ l per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

**[0683]** Results for 3 phage scFvs (I001C09, I018D07 and I016H07) that inhibited the binding of biotinylated BLyS are shown in Figure 2. Maximal binding of biotinylated BLyS to its receptor (bio-BLyS only), the background signal in the absence of biotinylated BLyS (no bio-BLyS), and results with an irrelevant (*i.e.*, does not recognize BLyS) phage antibody are also shown. All 3 phage scFvs inhibited biotinylated BLyS binding to its receptor on IM9 cells, identifying these scFvs as scFvs that bind the soluble form of BLyS. These scFvs also bind to U937 membranes, thus they also bind the membrane bound form of BLyS.

**[0684]** Forty-eight of the scFvs from panel 1 that demonstrated the greatest inhibition as phage particles in this assay were chosen for further study. These 48 scFvs are listed in Table 3.

Table 3. scFvs that Inhibit the Binding of Biotinylated-BLyS to its Receptor

Antibody	Antibody	Antibody	Antibody	Antibody
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I008C02	I029D07	I008C03	I008C12	I028A06
I022E02	I061E07	I007H08	I061H01	I031C03
I018C02	I006D07	I008A11	I006D08	I031F02
I008B01	I017D10	I061D02	I026E03	I031F09
I016F04	I007B03	I008A09	I027A07	I031G11
I016E05	I018C10	I007F11	I016H07	I050A07
I018H08	I001C09	I037E07	I021B05	I050A12
I018H09	I018D07	I037E12	I031G10	I050B11
	I029F11	I016F02	I031G08	I051C04
	I022D01		I031C07	I003F12
			I012A06	

#### Example 4: Specificity of Anti-BLyS Antibodies

**[0685]** The specificity of the 48 scFvs listed in Table 3 for human and murine BLyS was determined using phage ELISA.

#### Phage ELISA

**[0686]** To determine the specificity of the 48 scFvs, a phage ELISA was performed against human and mouse BLyS, and a panel of related and unrelated human antigens: Fas ligand, TRAIL, TNF $\alpha$ , TNF $\beta$ , and PBS. The : Fas ligand, TRAIL, TNF $\alpha$ , and TNF $\beta$  antigens were obtained from R&D Systems, Minneapolis, MN. Individual *E. coli* colonies containing phagemid were inoculated into 5 ml 2YTAG and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37°C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatant (5 ml) was carefully transferred to a fresh tube, 1 ml of 6MPBS was added, and the tube was incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

**[0687]** All antigens were coated at 1 µg/ml. ELISAs were performed essentially as described in Example 2. The only exception to this being the detection of phage antibody binding to mouse BLyS where the step involving incubation with the HRP-labelled anti-mouse polymer was omitted. Binding to mouse BLyS was detected with TMB as in Section Example 2.

**[0688]** All 48 scFvs are specific for immobilized human BLyS and 43 out of the 48 scFvs cross-react with immobilized mouse BLyS but not with any other unrelated or related antigen tested. I008C03, I007F11, I037E07, I037E12, and I016H07 did not bind murine BLyS. Results for two scFvs, I022D01 and I031F02, are shown in Figure 3. Both these scFvs specifically recognize human and mouse BLyS but not any other unrelated or related antigen tested.

#### Example 5: Specificity for the Membrane-Bound Form of BLyS

**[0689]** The specificity of 48 scFvs for membrane-bound BLyS was determined by the phage ELISA described in Example 2. BLyS was immobilised onto plastic as a membrane-bound form present on plasma membranes preparations from the human macrophage-like cell line, U937. This cell line is known to express the membrane-bound form of human BLyS.

**[0690]** To demonstrate that this binding is specific for membrane-bound BLyS, a competition ELISA was developed to determine if the ELISA signal for an individual antibody on U937's could be competed out by pre-incubation with either BLyS or TNFα. An anti-BLyS antibody that also recognizes membrane-bound BLyS would be expected to demonstrate a signal reduction with free BLyS but not free TNFα.

#### Competition ELISA

**[0691]** Individual *E. coli* colonies containing phagemid for each of the 48 scFvs listed in Table 3 were inoculated into 5 ml 2YTAg and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10

**[0687]** All antigens were coated at 1 µg/ml. ELISAs were performed essentially as described in Example 2. The only exception to this being the detection of phage antibody binding to mouse BLyS where the step involving incubation with the HRP-labelled anti-mouse polymer was omitted. Binding to mouse BLyS was detected with TMB as in Section Example 2.

**[0688]** All 48 scFvs are specific for immobilized human BLyS and 43 out of the 48 scFvs cross-react with immobilized mouse BLyS but not with any other unrelated or related antigen tested. I008C03, I007F11, I037E07, I037E12, and I016H07 did not bind murine BLyS. Results for two scFvs, I022D01 and I031F02, are shown in Figure 3. Both these scFvs specifically recognize human and mouse BLyS but not any other unrelated or related antigen tested.

#### Example 5: Specificity for the Membrane-Bound Form of BLyS

**[0689]** The specificity of 48 scFvs for membrane-bound BLyS was determined by the phage ELISA described in Example 2. BLyS was immobilised onto plastic as a membrane-bound form present on plasma membranes preparations from the human macrophage-like cell line, U937. This cell line is known to express the membrane-bound form of human BLyS.

**[0690]** To demonstrate that this binding is specific for membrane-bound BLyS, a competition ELISA was developed to determine if the ELISA signal for an individual antibody on U937's could be competed out by pre-incubation with either BLyS or TNFα. An anti-BLyS antibody that also recognizes membrane-bound BLyS would be expected to demonstrate a signal reduction with free BLyS but not free TNFα.

#### Competition ELISA

**[0691]** Individual *E. coli* colonies containing phagemid for each of the 48 scFvs listed in Table 3 were inoculated into 5 ml 2YTAG and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight with shaking. The next day, the cells were pelleted by



centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatants (5 ml) were carefully transferred to a fresh tube.

**[0692]** For each of the 48 scFvs listed in Table 3, two aliquots of 20  $\mu$ l 6xMPBS were pipetted into separate wells of a 96-well plate (Greiner). The first aliquot was supplemented with BLyS to a final concentration of 0.5  $\mu$ g/ml. The second aliquot was supplemented with TNF- $\alpha$  to a final concentration of 0.5  $\mu$ g/ml. Each experiment was performed in triplicate. One hundred  $\mu$ l of each phage supernatant was then added to each aliquot and mixed by pipetting up and down. The phage were incubated ( $\pm$  competing antigen) at room temperature for 1 hour.

**[0693]** Flexible 96-well plates (Falcon) were coated overnight at 4°C with 50  $\mu$ l of 10  $\mu$ g/ml U937 plasma membranes. After coating, the plates were washed 3 times with PBS and blocked for 1 hour at room temperature with 200  $\mu$ l MPBS. The plates were washed 3 times with PBS and 50  $\mu$ l of phage ( $\pm$  competing antigen) was added to each appropriate well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50  $\mu$ l of a mouse anti-gene VIII-HRP conjugate (Pharmacia) at a 1:5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50  $\mu$ l of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1:50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty  $\mu$ l of TMB substrate was then added to each well, and incubated at room temperature for 30 to 60 minutes or until color development. The reaction was stopped by the addition of 25  $\mu$ l of 0.5 M H<sub>2</sub>SO<sub>4</sub>. The signal generated was measured by reading the absorbance at 450nm (A<sub>450</sub>) using a microtiter plate reader (Bio-Rad 3550).

**[0694]** All 48 scFvs bind to U937 plasma membrane preparations. This signal could be competed out by pre-incubation of the phage antibody with BLyS but not by pre-incubation with TNF- $\alpha$ . This indicates that the 48 scFvs specifically recognize membrane-bound BLyS as well as soluble BLyS. Typical results are exemplified by scFvs I031F09, I050A12 and I051C04 and are shown in Figure 4. All 3 scFvs demonstrate binding to U937 plasma membranes. This binding was specifically competed

out with BLyS but did not compete with TNF- $\alpha$ , demonstrating specific recognition of membrane-bound BLyS.

#### Example 6: scFv Off-rate Determinations

**[0695]** All off-rate determinations were performed on BIAcore 2000 machines, using the BIAcore 2000 Control Software and evaluated using the BIAevaluation 3.0 software.

#### Preparation of a Low Density BLyS Surface

**[0696]** A 500RU surface was prepared for kinetic studies with purified scFvs. A low density BLyS surface (500 RU BLyS coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram initiated with HBS buffer at a flow rate of 5  $\mu$ l/min. The NHS and EDC coupling solutions (BIAcore) were mixed according to manufacturer's instructions and 30  $\mu$ l injected over the CM5 surface. Fifty  $\mu$ l of BLyS at 1  $\mu$ g/ml in 10 mM sodium acetate buffer, pH4, was then injected followed by 30  $\mu$ l of ethanolamine-HCl solution (BIAcore). The flow rate was then adjusted to 20  $\mu$ l/min and 10  $\mu$ l of 4M guanidine hydrochloride in HBS injected over the surface. This strips the surface of non-covalently bound BLyS.

#### Measurement of scFv off-rate kinetics on the low density surfaces

**[0697]** The chip containing the low density BLyS surface was inserted in to the BIAcore. A dilution series of purified scFvs was prepared in HBS, typically 50  $\mu$ g/ml doubling dilutions down to 1.5  $\mu$ g/ml. The dilution series was then injected sequentially over the low density BLyS surface (and blank control) using the following program:

MAIN

FLOWCELL 1,2,3,4

APROG	genab	r1d1	ab1
APROG	genab	r1d2	ab2
APROG	genab	r1d3	ab3
APROG	genab	r1d4	ab4

APROG	genab	r1d5	ab5
APROG	genab	r1d6	ab6

APPEND CONTINUE

END

DEFINE APROG genab

PARAM %Abpos %AbId

FLOW 20

KINJECT %Abpos 200 80

INJECT r1c6 10!guanine hydrochloride regeneration step

EXTRACLEAN

END

**[0698]** Bound scFvs were removed by injecting 10µl 4M GuHCl in HBS over the surface between scFv samples.

**[0699]** The binding curves for individual scFvs were analyzed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I003C02, is shown in Figure 5. I003C02 has a  $K_{off} = 6 \times 10^{-3} \text{ s}^{-1}$ .

Example 7: Inhibition in an *In Vitro* Receptor Binding Assay by scFv Antibodies

**[0700]** The 48 scFvs listed in Table 3 were purified and assessed for their ability to inhibit BLyS binding to its receptor on IM9 cells.

#### Purification of scFv

**[0701]** To determine the inhibitory potency of anti-BLyS scFv, scFv's were first prepared by IMAC. 2TYAG (5 ml) was inoculated with a single colony and grown overnight at 30°C, shaking. This overnight culture was then used to inoculate 500 ml of 2TY containing 100 µg/ml ampicillin and 0.1% Glucose, and grown at 30° C, shaking, until an  $A_{600}$  of 1.0 was attained. IPTG was added to 1 mM and the culture was grown for a further 3.5 hours at 30°C.

[0702] Cells were harvested by centrifugation at 5,000rpm, and resuspended in 10 ml of TES. A further 15 ml of a 1:5 dilution (in water) of TES was added, and the cell suspension incubated on a turning wheel at 4°C for 30 minutes. This causes osmotic shock and yields a periplasmic extract containing the scFv. Residual cells and debris were pelleted by centrifugation at 9,000 rpm for 20 minutes at 4°C. The supernatant was transferred to a new tube, and 50 µl of 1 M MgCl<sub>2</sub> added. Two ml of a Ni-NTA agarose (Qiagen), pre-washed with buffer (50 mM sodium phosphate, pH 8, 300 mM NaCl) together with a protease inhibitor tablet (Boehringer Mannheim) were then added to the periplasmic extract. The preparation was incubated, rotating, overnight at 4°C. The Ni-NTA was pelleted by centrifugation at 2,000 rpm for 5 minutes, and the supernatant was aspirated. The agarose beads were washed 3 times with 50 ml wash buffer, centrifuging to collect the agarose in between each wash. Ten ml of wash buffer was added after the final wash, and the slurry was loaded on to a polyprep column (BioRad). Two ml elution buffer (50 mM NaPi (sodium phosphate), pH 8, 300 mM NaCl, 250 mM imidazole) was added to the drained agarose, and the eluate was collected. IMAC purified scFv was buffer exchanged in to PBS by use of a Nap 5 column (Pharmacia) according to the manufacturer's instructions. The A<sub>280</sub> was read and the protein concentration determined using a molar extinction coefficient of 1 mg/ml protein = A<sub>280</sub> 1.4. Purified scFv was stored in 500 µl aliquots at -70°C.

#### Receptor Binding Inhibition Assay

[0703] Flat-bottomed 96-well plates (Costar) were coated with 100 µl per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4 °C overnight. One hundred µl of IM9 cells (at 10<sup>5</sup>/ml in RPMI-1640) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200 µl of MPBS added to each well. The plates were then left to block for 1 hour at room temperature.

[0704] To a separate 96-well plate, titrate test scFvs in MPBS, in triplicate, over a concentration range from 10 µg/ml down to 0.001 µg/ml were added. The final volume of test scFv in each well was 55 µl. Competition with unlabelled BLyS was also included in every assay as a control. Unlabelled BLyS, in MPBS, was typically titrated in triplicate,

over a concentration range from 1  $\mu\text{g/ml}$  down to 0.001  $\mu\text{g/ml}$ . 10  $\mu\text{l}$  of biotinylated-BLyS (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Plates were then incubated at room temperature for 30 minutes.

**[0705]** The IM9 coated plates was washed twice in PBS, tapped dry and immediately 50 $\mu\text{l}$  of the scFv/biotinylated-BLyS mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50  $\mu\text{l}$  per well added of streptavidin-Delfia (Wallac) at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100 $\mu\text{l}$  per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

**[0706]** Typical titration curves for two scFv antibodies, I007F11 and I050A07, are shown in Figure 6. Unlabelled BLyS competed for binding to its receptor with an  $\text{IC}_{50}$  value of 0.8 nM. The  $\text{IC}_{50}$  values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 9 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 4. This data also confirms that these 9 scFvs recognize the soluble form of BLyS.

Table 4: 9 ScFvs that demonstrated greatest potency in BLyS Receptor Binding Inhibition Assay

ScFv Antibody
I017D10
I022D01
I008A11
I006D08
I031F02
I050A12
I050B11
I051C04

### Example 8: Antibodies recognizing a soluble form of BLyS

**[0707]** A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble but not the membrane-bound forms of BLyS.

**[0708]** A phage library was screened for the ability to bind to biotinylated BLyS. The phage were exposed to biotinylated BLyS, allowed an interval of time to bind the biotinylated BLyS. Phage binding bio-BLyS were then isolated by capture on streptavidin coated magnetic beads.

**[0709]** The phage identified in the screen above (capture of Bio-BLyS from solution) were then screened by ELISA for their ability to bind immobilized BLyS. The scFv expressed by phage that bound immobilized BLyS were then cloned and sequenced. Again, several sequences were identified multiple times, thus a panel (panel 2) consisting of one example of each phage expressing a unique scFv was then characterized further.

**[0710]** The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V<sub>H</sub> and V<sub>L</sub> segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, [www.mrc-cpe.cam.ac.uk](http://www.mrc-cpe.cam.ac.uk)) and the closest germline identified.

### Example 9: Specificity For Soluble BLyS

**[0711]** The scFvs were isolated from a library of phage based on their ability to bind a soluble form of BLyS. Briefly, phage were preincubated with biotinylated BLyS in solution. Phage that bound to this biotinylated BLyS were then isolated using streptavidin coated magnetic beads.

**[0712]** The specificity of each of the unique scFvs for BLyS and for the membrane-bound form of BLyS, was determined by phage ELISA. BLyS was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937. Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

### Phage ELISA

**[0713]** To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against human BLyS, U937 plasma membranes, TNF $\alpha$ , BSA and an uncoated well. Antigen coating conditions were as described in Example 2, apart from human BLyS. BLyS was first biotinylated (as described in Example 3) and coated at 1  $\mu$ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

**[0714]** The results for 3 clones (I074B12, I075F12 and I075A02) that bind the soluble but not the membrane-bound form of BLyS are shown in Figure 7. As a control, a phage antibody that recognizes TNF $\alpha$ , is also shown in Figure 7. There is a small non-specific background signal on the U937 plasma membranes that is evident with both the anti-BLyS scFvs as well as the anti-TNF $\alpha$  control. All 3 anti-BLyS scFvs recognize BLyS but not U937 plasma membranes, TNF $\alpha$ , BSA or an uncoated well (PBS only). This indicates that the scFvs do not bind the membrane-bound form of BLyS. Further, The fact that these scFvs were isolated on the basis of their ability to bind soluble biotinylated BLyS indicates that they bind the soluble form of BLyS. Further confirmation of these scFvs' specificity for BLyS is provided in Example 10.

Example 10: Inhibition in an *in vitro* receptor binding assay by phage scFvs

**[0715]** All of the unique phage scFvs from panel 2 were assessed for their ability to inhibit BLyS binding to its cognate receptor on IM9 cells. The biotinylation of BLyS, maintenance of IM9 cells and receptor binding inhibition assay were performed as described in Example 3.

**[0716]** Results for two phage scFvs, I0025B09 and I026C04 are shown in Figure 8. Maximal binding of biotinylated BLyS to its receptor (bio-BLyS only), the background signal in the absence of biotinylated BLyS (no bio-BLyS), and results with an irrelevant (i.e. does not recognize BLyS) phage antibody are also shown. Both phage scFvs inhibited biotinylated BLyS binding to its receptor on IM9 cells. 33 of the unique scFvs from panel 2 were identified for further study. These 33 scFvs demonstrated the greatest inhibition as phage particles in this assay and are listed in Table 5.

Table 5: Identification of 33 phage scFvs to free BLyS that demonstrate the most significant inhibition of biotinylated-BLyS binding to its receptor

Antibody	Antibody	Antibody	Antibody
I026C04	I074B12	I073F04	I065D04
I003C06	I075A02	I078D08	I068C08
I025B09	I068B08	I078D02	I068F03
I027B12	I068B04	I075G01	I069B07
I025B06	I068C06	I071B03	
I030A10	I075F12	I072B09	
I002A01R	I065D08	I078H08	
I002A01K	I065F08	I064C04	
I026C04R	I067B10	I064C07	
I026C04K	I067F05		

#### Example 11: Specificity of anti-BLyS scFvs

**[0717]** The specificity of the 33 scFvs (listed in Table 5) for immobilized human and murine BLyS was determined using phage ELISA.

#### Phage ELISA

**[0718]** To determine the specificity of the 33 scFvs, a phage ELISA was performed as described in Example 4 against human and mouse BLyS, and a panel of related human antigens: TRAIL, LIGHT, TNF $\alpha$ , TNF $\beta$ , and an uncoated well (PBS only).

**[0719]** Typical results for two scFvs, I067F05 and I078D02 are shown in Figure 9. A control antibody that specifically recognizes TNF $\alpha$  is also shown. Both anti-BLyS scFvs specifically recognize immobilized human and mouse BLyS but not any other antigen tested.

**[0720]** All 33 scFvs are specific for human BLyS. 14/33 cross-react with mouse BLyS but not with any other unrelated or related antigen tested.

#### Example 12: scFv Off-Rate Determinations

**[0721]** Off-rate determinations, preparation of a low density BLyS surface and kinetic measurements were as detailed in Example 6.

**[0722]** The binding curves for individual scFvs were analysed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I002A01, is shown in Figure 10. I002A01 has a  $K_{\text{off}} = 9 \times 10^{-4} \text{ s}^{-1}$ .



Example 13: Inhibition in an *in vitro* receptor binding assay by scFv antibodies

**[0723]** The 33 scFvs identified in Table 5 were prepared as purified scFvs and assessed for their ability to inhibit BLYS binding to its receptor on IM9 cells. The scFvs were purified and analysed in the receptor binding inhibition assay as described in Example 6.1.8.

**[0724]** Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLYS competed for binding to its receptor with an inhibitory constant 50 ( $IC_{50}$ ) value of 0.66 nM. The  $IC_{50}$  values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 7 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 6.

Table 6: Identification of 7 scFvs to free BLYS that demonstrate the most significant inhibition of biotinylated-BLYS binding to its receptor as purified scFv's.

Antibody
I002A01-R
I002A01-K
I026C04-R
I026C04-K
I068C06
I075F12
I067B10

Example 14: ScFvs Recognizing Membrane-bound BLYS

**[0725]** A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the membrane-bound but not the soluble form of BLYS.

**[0726]** As a starting point, a library of phage expressing scFv antibodies were panned on immobilized HIS-tagged BLYS. Phage isolated by panning were then screened for the ability to bind to HIS-tagged BLYS. HIS-tagged BLYS was obtained by expressing amino acids 71-285 of SEQ ID NO:3228 using the pQE9 vector (Qiagen Inc.,

Valencia, CA) in *E. coli* and purifying the expressed protein. This phage clones identified by this screen were then sequenced. After sequencing, A panel (panel 3) of phage each expressing a unique scFv that bound HIS-tagged BLyS was generated and further characterized.

**[0727]** The derived amino acid sequences of the unique scFvs from panel 3 are shown in Table 1 above. The individual V<sub>H</sub> and V<sub>L</sub> segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mrc-cpe.cam.ac.uk) and the closest germline identified.

#### Example 15: Recognition of Membrane-bound BLyS

**[0728]** The specificity of each of the unique scFvs for both the membrane-bound form of BLyS as well as for the soluble form of BLyS, was determined by phage ELISA.

**[0729]** BLyS was immobilised onto plastic either directly as a purified soluble form of the protein or biotinylated and coated on a streptavidin plate as in Example 9. Binding to HIS-tagged BLyS was used as a primary screen for scFv's that would bind the membrane-bound form of BLyS (see below). The membrane-bound form of BLyS was presented as plasma membranes preparations from the human macrophage-like cell line, U937 or the murine cell line P388.

**[0730]** Mouse monoclonal antibodies have been raised against His-tagged BLyS according to standard procedures. Characterization of these mouse monoclonal antibodies revealed that they specifically recognized both His-tagged BLyS and the membrane-bound form of BLyS on U937 cells, but not soluble BLyS. Therefore, specific recognition of His-tagged BLyS was used as supporting evidence for the recognition of the membrane-bound form of BLyS by phage and scFv antibodies.

#### Phage ELISA

**[0731]** To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against His-tagged human BLyS, U937 plasma membranes, TNF $\alpha$ , BSA and an uncoated well. Antigen coating conditions were as described in 2. apart from human BLyS. BLyS was first biotinylated (as described in Example 3) and coated at 1  $\mu$ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as

detailed in Example 2.

**[0732]** The results for 3 clones, I079C01, I081C10 and I082A02, and a control phage antibody that recognizes TNF $\alpha$ , are shown in Figure 12. All 3 scFvs recognize U937 plasma membranes (U937) and His-tagged BLYS (HIS-BLYS) but not, biotinylated BLYS (bio-BLYS) or an uncoated well (PBS). This indicates that the scFvs recognize the membrane-bound form of BLYS.

#### Example 16: Specificity for Membrane-bound BLYS

**[0733]** The specificity of the scFvs for only the membrane-bound form of BLYS, and not for the soluble form, was confirmed using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of BLYS on U937 plasma membranes in the presence of different forms of competing BLYS. Competing BLYS was either the His-tagged form of BLYS or soluble BLYS. ScFvs specific for the membrane-bound BLYS would be expected to be competed out by pre-incubation with His-tagged BLYS but not by pre-incubation with soluble BLYS.

**[0734]** Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

#### Competition ELISA

**[0735]** U937 plasma membranes (50 $\mu$ l per well ) were coated at 10 $\mu$ g/ml in PBS onto Falcon 96-well plates overnight at 4°C.

**[0736]** Individual E. coli colonies containing a phagemid representing one of the unique scFvs from the panel 3 were inoculated into 50 ml tubes (Falcon) containing 5 ml 2TYAG medium. Tubes were incubated at 37°C for 4 hours, shaking. M13KO7 helper phage was added to each tube to an MOI of 10 and the tubes were incubated for a further 1 hour at 37°C. The tubes were centrifuged in a benchtop centrifuge at 3500 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight, shaking. The next day, tubes were centrifuged at 3500 rpm for 10 min and the phage-containing supernatant carefully transferred into a fresh tube.

**[0737]** For each test phage antibody, 3 aliquots of 20 $\mu$ l 18% marvel/6xPBS were transferred into separate wells of a 96-well plate. The first aliquot was supplemented with

His-tagged BLyS to a final concentration of 60 µg/ml. The second aliquot was supplemented with soluble BLyS to a final concentration of 60 µg/ml. The third aliquot was not supplemented with any competing antigen. One hundred µl of phage supernatant was then added to each aliquot and left to block at room temperature for 1 hour.

**[0738]** The antigen-coated plates were washed once with PBS before the addition of 200 µl/well 3% marvel/PBS. These plates were left to block at 37°C for 1 hour and were then washed once with PBS. Duplicate samples of 50 µl pre-blocked phage (above) were added to the antigen-coated plates and left at room temperature for 1 hour. Plates were washed 3x with PBS/0.1%Tween 20, then 3x with PBS. Fifty µl/well mouse anti-M13 HRP (Pharmacia) at 1/5000 in 3% Marvel/PBS was added and left for 1 hour at room temperature. Plates were washed 3 times with PBS/0.1%Tween 20, then 3 times with PBS. Fifty µl/well HRP-labelled anti-mouse Envision polymer (DAKO) at 1/50 in 3% marvel/PBS was added and left for 1 hour at RT. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Next, 50µl/well of TMB (Sigma) was added and plates left to develop for 30 to 60 minutes. When sufficient color has developed, 25µl/well 0.5M H<sub>2</sub>SO<sub>4</sub> was added to stop the reaction. The plates were read at 450nm on a microtiter plate reader (Bio-Rad 3550).

**[0739]** The results for 3 clones, I079B04, I079F08 and I080B01, and a control phage antibody that recognizes TNFα, are shown in Figure 13. All 3 scFvs recognize U937 plasma membranes (U937). This binding is competed out to background levels (i.e. comparable to the signal observed with the anti-TNFα phage antibody) in the presence of His-tagged BLyS (HIS-BLyS) but not biotinylated BLyS (bio-BLyS). This confirms that the scFvs specifically recognize the membrane-bound form but not the soluble form of BLyS.

Example 17: High Throughput BIAcore Screen to identify high affinity scFvs

**[0740]** This is a 96-well screen where the test samples (scFvs) are derived from 1 ml periplasmic extracts of individual antibody expressing clones. Potentially higher affinity scFvs are then identified principally as those giving a large number of total RU's bound to a HIS-BLyS surface in BIAcore. This method of ranking does assume approximately equal yields of scFv from each clone. Since this is not always the case,

some scFvs may also be identified that simply express high levels of scFv. These can be discriminated from those of higher affinity by further characterization of the scFvs (see Example 18).

#### Preparation of ScFv from 1ml E.coli Cultures

**[0741]** Individual E.coli colonies containing a phagemid representing one of the unique scFvs from panel 3 were inoculated into 96-well plates containing 100  $\mu$ l 2TYAG medium per well. Eight wells on each plate were reserved for positive and negative control samples. The plate was grown overnight at 30°C with shaking at 120 rpm.

**[0742]** Next day, 1ml of 2TYAG + 345 mM sucrose was added to each well of an autoclaved 96 deep well plate (Beckman). Twenty  $\mu$ l of each overnight culture was resuspended and transferred to the appropriate well of the deep well plate. The plate was grown for approximately 3.5 hours at 30°C with shaking at 250 rpm (or until the OD<sub>600</sub> = 0.6). Fifty  $\mu$ l of 1M IPTG was added to 5ml 2TY and 10 $\mu$ l of this was added to each well. The plate was grown overnight at 30°C with shaking at 250rpm.

**[0743]** Plates were kept at 4°C for the remainder of the procedure. The overnight plate (above) was centrifuged at 3500 rpm for 10 minutes at 4°C to pellet the cells. The supernatant was decanted and each pellet resuspended in 100 $\mu$ l TES (0.2M Tris HCl pH8.0, 0.5mM EDTA, 0.5M sucrose) and transferred to a fresh 96 well plate. This plate was incubated on ice for 30 minutes and then centrifuged for 10 minutes at 3500 rpm at 4°C to pellet the cell debris. During centrifugation, 15 $\mu$ l of freshly made protease inhibitors cocktail (Roche, 1 tablet dissolved in 1.5 ml water) was added to each well of a fresh 96 well plate. Supernatants from the centrifuged plate were then transferred to the plate containing the protease inhibitors. The plate was centrifuged at 3500 rpm for 10 minutes at 4°C and the supernatant was transferred to a further 96-well plate. This step was repeated at least once more or until there was no sign of any cell debris following centrifugation. Finally, the plate was covered in foil to prevent evaporation of samples during the BIAcore run.

#### Generation of a high density HIS-BLyS surface

**[0744]** All BIAcore analysis was performed on BIAcore 2000 machines, using the BIAcore 2000 control software and evaluated using the BIAevaluation 3.0 software. A

high density His-tagged BLyS surface (>1000 RU HIS-BLyS coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram started over flow cell 2 with HBS buffer at a flow rate of 5µl/min. The NHS and EDC solution were mixed 1:1 before injecting 30µl over the CM5 surface. Fifty µl HIS-BLyS (at 10µg/ml in Sodium acetate buffer, pH4) was injected and allowed to couple to the surface. Thirty µl of ethanolamine-HCl solution was then injected to block free NHS esters. Prior to using the chip, 10µl of 4M Guanidine hydrochloride in HBS was injected over the surface to strip the surface of non-covalently bound BLyS. A blank surface (no HIS-BLyS) was also prepared over flow cell 1 so that non-specific binding effects can be subtracted from the HIS-BLyS binding curves.

**[0745]** Typically, a 5000 RU His-tagged BLyS surface was generated in this way and used for 96-well analysis of scFvs isolated from the periplasm of E.coli.

#### BIAcore Analysis

**[0746]** The 96-well plate containing periplasmic scFvs was secured inside the BIAcore. Two ml of 4M Guanidine hydrochloride in HBS was placed in a rack inside the BIAcore for regeneration of the HIS-BLyS surface between samples. The sensorgram was run over flow cells 1 and 2 at a flow rate of 20µl/minute. The following method was run:

#### MAIN

FLOWCELL 1,2,3,4

LOOP cycle STEP

APROG inj %pos

ENDLOOP

APPEND CONTINUE

END

DEFINE LOOP cycle

LPARAM %pos

antibody comprising, or alternatively consisting of, a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind BLyS and comprise, or alternatively consist of, fragments or variants of the VL and/or domains and/or VHCDR(s) and/or VLCDR(s) are also encompassed by the invention.

[0240] The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the VH domains, VH CDRs, VL domains, and VL CDRs described herein, which antibodies immunospecifically bind to BLyS. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants

can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind BLyS). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to immunospecifically bind BLyS) can be determined using techniques described herein or by routinely modifying techniques known in the art.

**[0241]** The antibodies of the invention include derivatives (i.e., variants) that are modified, e.g., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not affect the ability of the antibody to immunospecifically bind to BLyS. For example, but not by way of limitation, derivatives of the invention include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

**[0242]** In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains referred to in Table 1 under stringent conditions, e.g., hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, e.g., hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody of the invention that immunospecifically binds to BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that



encoding one of the VH CDRs or VL CDRs referred to in Table 1 under stringent conditions, *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDR3s referred to in Table 1 under stringent conditions *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0243]** In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0244]** In another embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least

50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0245]** Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding affinity for to BLyS polypeptides or fragments or variants of BLyS polypeptides (e.g., to the soluble form of BLyS and/or membrane-bound form of BLyS). In specific embodiments, antibodies of the invention bind BLyS polypeptides, or fragments or variants thereof, with a dissociation constant or  $K_D$  of less than or equal to  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M, or  $10^{-5}$  M. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M, or  $10^{-8}$  M. Even more preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M. The invention encompasses antibodies that bind BLyS polypeptides with a dissociation constant or  $K_D$  that is within any one of the ranges that are between each of the individual recited values.

**[0246]** In specific embodiments, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an off rate ( $k_{off}$ ) of less than or equal to

$5 \times 10^{-2} \text{ sec}^{-1}$ ,  $10^{-2} \text{ sec}^{-1}$ ,  $5 \times 10^{-3} \text{ sec}^{-1}$  or  $10^{-3} \text{ sec}^{-1}$ . More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an off rate ( $k_{\text{off}}$ ) less than or equal to  $5 \times 10^{-4} \text{ sec}^{-1}$ ,  $10^{-4} \text{ sec}^{-1}$ ,  $5 \times 10^{-5} \text{ sec}^{-1}$ , or  $10^{-5} \text{ sec}^{-1}$   $5 \times 10^{-6} \text{ sec}^{-1}$ ,  $10^{-6} \text{ sec}^{-1}$ ,  $5 \times 10^{-7} \text{ sec}^{-1}$  or  $10^{-7} \text{ sec}^{-1}$ . The invention encompasses antibodies that bind BLyS polypeptides with an off rate ( $k_{\text{off}}$ ) that is within any one of the ranges that are between each of the individual recited values.

**[0247]** In other embodiments, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an on rate ( $k_{\text{on}}$ ) of greater than or equal to  $10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $10^4 \text{ M}^{-1} \text{ sec}^{-1}$  or  $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ . More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an on rate ( $k_{\text{on}}$ ) greater than or equal to  $10^5 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $10^6 \text{ M}^{-1} \text{ sec}^{-1}$ , or  $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$  or  $10^7 \text{ M}^{-1} \text{ sec}^{-1}$ . The invention encompasses antibodies that bind BLyS polypeptides with on rate ( $k_{\text{on}}$ ) that is within any one of the ranges that are between each of the individual recited values.

**[0248]** The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By “biological characteristics” is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to bind to BLyS (e.g., the soluble form of BLyS, the membrane-bound form of BLyS, the soluble form and membrane-bound form of BLyS), and/or an antigenic and/or epitope region of BLyS), the ability to substantially block BLyS/BLyS receptor (e.g., TACI - GenBank accession number AAC51790 and/or BCMA -GenBank accession number NP\_001183) binding, or the ability to block BLyS mediated biological activity (e.g., stimulation of B cell proliferation and immunoglobulin production). Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

**[0249]** The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that neutralize BLyS or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv referred to in Table 1, more

preferably having an amino acid sequence contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908, and even more preferably having an amino acid sequence contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "neutralizes BLYS or a fragment thereof" is meant an antibody that diminishes or abolishes the ability of BLYS to bind to its receptor (e.g., TACI and BCMA) to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLYS receptor signalling cascade. In one embodiment, an antibody that neutralizes BLYS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLYS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLYS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that neutralizes BLYS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLYS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes BLYS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0250]** The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLyS mediated B cell proliferation as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (e.g., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 - 1908, and even more preferably having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0251]** The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that enhance the activity of BLyS or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (i.e., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908, and preferably having an

amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885, as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "enhances the activity of BLyS or a fragment thereof" is meant an antibody increases the ability of BLyS to bind to its receptor (e.g., TACI or BCMA), to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLyS receptor signalling cascade. In one embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0252]** The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that

stimulate BLyS mediated B cell proliferation as determined by any method known in the art, such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (e.g., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence of SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908, and even more preferably having an amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

**[0253]** The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically binds to BLyS, and a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused to is useful for B-cell function or is useful to target the antibody to B-cells. In an alternative preferred embodiment, the heterologous polypeptide to which the antibody is fused to is useful for monocyte cell function or is useful to target the antibody to a monocyte. In another embodiment, the heterologous polypeptide to which the

antibody is fused is albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

**[0254]** In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains referred to in Table 1 or the amino acid sequence of any one or more of the VL domains referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1, or the amino acid sequence of any one, two, three, or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 referred to in Table 1, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein immunospecifically binds to BLYS. In another embodiment, a fusion protein



comprises, or alternatively consists of a polypeptide having the amino acid sequence of at least one VH domain referred to in Table 1 and the amino acid sequence of at least one VL domain referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, the VH and VL domains of the fusion protein correspond to the same scFv referred to in Table 1. In yet another embodiment, a fusion protein of the invention comprises, or alternatively consists of a polypeptide having the amino acid sequence of any one, two, three or more of the VH CDRs referred to in Table 1 and the amino acid sequence of any one, two, three or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the VHCDR(s) or VLCDR(s) correspond to the same scFv referred to in Table 1. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

**[0255]** The present invention also provides: antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically bind to the soluble form of BLyS; antibodies that immunospecifically bind to the membrane-bound form of BLyS; and antibodies that immunospecifically bind to both the soluble form and membrane-bound form of BLyS.

**[0256]** In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form of BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1563 – 1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) (including derivative) thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained SEQ ID NOS: 1563 - 1880 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs

of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form of BLYS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0257] In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the membrane-bound form of BLYS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the membrane-bound form of BLYS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the membrane-bound form of BLYS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also

encompassed by the invention.

**[0258]** In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form and membrane-bound form of BLyS, are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1 - 1562, disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1 - 1562, disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1.

**[0259]** The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for mixtures of different antibodies that immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the membrane-bound form and soluble form of BLyS. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at

least 12, at least 15, at least 20, or at least 25 different antibodies that immunospecifically bind to BLYS, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

**[0260]** The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLYS, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for panels of different antibodies that immunospecifically bind to the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the membrane-bound form and soluble form of BLYS. In specific embodiments, the invention provides for panels of antibodies that have different affinities for BLYS, different specificities for BLYS, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

**[0261]** The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant

thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1563 - 1880, as disclosed in Table 1 or a variant thereof.

**[0262]** The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 or a variant thereof.

**[0263]** The present invention further provides for compositions comprising, one or more antibodies (including scFvs, or molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof.

In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 or a variant thereof.

**[0264]** Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof.

**[0265]** Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a

polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof.

**[0266]** Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more

of the VL CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof.

**[0267]** In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains disclosed in Table 1, or a variant thereof, and an amino acid sequence of any one or more of the VL domains disclosed in Table 1, or a variant thereof wherein the VH and VL domains are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLyS (SEQ ID NOS:1563 - 1880), from scFvs that bind membrane-bound BLyS (SEQ ID 1881 - 2128), or from scFvs that bind both soluble and membrane-bound BLyS (SEQ ID NOS:1 - 1562). In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1,2, or 3) and VL CDRY (where Y= 1,2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLyS (SEQ ID NOS:1563 - 1880), from scFvs that bind membrane-bound BLyS (SEQ ID NOS:1881 - 2128), or from scFvs that bind both soluble and membrane-bound BLyS (SEQ ID NOS:1 - 1562). In yet another embodiment, a composition of the present invention comprises one or more fusion proteins.

**[0268]** As discussed in more detail below, a composition of the invention may be used either alone or in combination with other compositions. The antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

**[0269]** Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may be used, for example, but not limited to, to purify and detect BLyS, and to target the polypeptides of the present invention to cells expressing membrane-bound BLyS or BLyS receptor, including both *in vitro* and *in vivo* diagnostic and therapeutic methods.



For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of BLyS in biological samples. See, *e.g.*, Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

#### Methods Producing Antibodies

[0270] The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[0271] The single chain Fvs disclosed in Table 1 were generated using phage display methods known in the art. Furthermore, other scFvs that immunospecifically bind BLyS may be generated using phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of lymphoid tissues) or synthetic cDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (*e.g.*, p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (*i.e.*, BLyS or a fragment thereof) can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman *et al.*, *J. Immunol. Methods* 182:41-50 (1995); Ames *et al.*, *J. Immunol. Methods* 184:177-186 (1995); Kettleborough *et al.*, *Eur. J. Immunol.* 24:952-958 (1994); Persic *et al.*, *Gene* 187 9-18 (1997); Burton *et al.*, *Advances in Immunology* 57:191-280(1994); PCT application No. PCT/GB91/O1 134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/1 1236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Patent Nos. 5,698,426; 5,223,409;

5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

**[0272]** As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax *et al.*, *BioTechniques* 12(6):864-869 (1992); Sawai *et al.*, *AJRI* 34:26-34 (1995); and Better *et al.*, *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

**[0273]** To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

**[0274]** Cell lines that express antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCC") on the dates listed in Table 2 and given the ATCC Deposit Numbers identified in Table 2. The ATCC is located at 10801 University Boulevard, Manassas, VA 20110-

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APROG      genab      r1d4  ab4
APROG      genab      r1d5  ab5
APROG      genab      r1d6  ab6

```

APPEND CONTINUE

END

```

DEFINE APROG genab
PARAM %Abpos %AbId
FLOW      20
KINJECT   %Abpos 200 80
INJECT    r2f3 10
EXTRACLEAN
END

```

**[0752]** Bound scFv were removed by injecting 10µl of 4M Guanidine hydrochloride in HBS (location r2f3 in the above program) over the surface between samples. Binding curves for individual scFv were analysed using the BIAevaluation software to determine antibody on- and off-rates.

**[0753]** A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as  $2 \times 10^{-3} \text{ s}^{-1}$ . The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv. The 5 scFvs with the highest affinities as scFvs are given in Table 8.

Table 8: Identification of 5 antibodies to membrane-bound BLyS that have the highest affinities as scFvs

Antibody	Affinity (K <sub>D</sub> )
I079F11	5nM
I079E02	10nM
I082G02	6nM
I082H08	1nM
I099D03	4nM

Example 19: Recognition of mouse membrane-bound BLYS

**[0754]** The ability of the 5 scFvs listed in Table 8 to also recognize murine membrane-bound BLYS was determined using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of BLYS on the murine cell line, P388, plasma membranes in the presence of different forms of competing human BLYS. Competing BLYS was either presented as the His-tagged form of BLYS, or soluble BLYS. ScFvs that recognize mouse membrane-bound BLYS would give an ELISA signal on the P388 plasma membranes that is competed out by pre-incubation with HIS-tagged BLYS but not by pre-incubation with soluble BLYS.

#### Maintenance of P388.D1 cells and preparation of plasma membranes

**[0755]** P388.D1 cells are a mouse monocyte-macrophage like cell line. They were cultured in L-15 medium supplemented with 2mM L-glutamine, 10% CS, 10U penicillin, 100g/ml streptomycin (all reagents from Sigma). Cells were split 1:4 every 3-4 days to maintain a cell density of  $2-8 \times 10^5$  per ml. A fresh aliquot of cells was thawed from liquid nitrogen every 6 weeks. Plasma membrane fractions were prepared as described in Example 2.

#### Competition ELISA

**[0756]** P388 plasma membranes (50 $\mu$ l per well ) were coated at 10 $\mu$ g/ml in PBS onto Falcon 96-well plates overnight at 4°C. The method is otherwise essentially as described Example 16.

**[0757]** The results for 3 clones, I079E02, I082H08 and I099D03 are shown in Figure 16. All 3 scFvs recognize P388 plasma membranes. This binding is competed out in the presence of HIS-tagged BLYS (HIS-BLYS) but not in the presence of biotinylated BLYS (bio-BLYS). This confirms that these scFvs also recognize the membrane-bound form but not the soluble form of mouse BLYS.

Example 20 : Conversion of scFvs to IgG1 format

**[0758]** The VH domain and the VL domains of scFvs that we wished to convert

into IgG molecules were cloned into vectors containing the nucleotide sequences of the appropriate heavy (human IgG1) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods for converting scFvs into conventional antibody molecules are well known within the art.

#### Generation of NS0 cell lines expressing anti-BLyS antibodies (IgG1)

**[0759]** Plasmids containing the heavy and light chains were separately linearized using the Pvu I restriction enzyme. The linearized DNAs were purified by phenol-chloroform extraction followed by ethanol precipitation and then resuspended in H<sub>2</sub>O. NS0 cells ( $10^7$ ) from a growing culture were electroporated (0.25kV and 975 $\mu$ F) in PBS with 12.5  $\mu$ g linearized heavy chain plasmid DNA and 37.5  $\mu$ g linearized light chain DNA. The cells were washed in 20 ml non-selective medium (10% FCS in DMEM supplemented with 6mM glutamine, amino acids and penicillin/streptomycin) and then transferred in 12.5 ml medium into a T75cm<sup>2</sup> flask and incubated overnight at 37 °C, 5% CO<sub>2</sub>/air. The day after transfection the cells were resuspended in selective medium containing 1mg/ml geneticin and dispensed into 5 x 96-well plates at 200  $\mu$ l/well. After 18 days at 37 °C (5% CO<sub>2</sub>/air) the colony supernatants were screened by an ELISA that detects assembled human IgG in order to identify colonies expressing IgG. Approximately twenty positive colonies were expanded and adapted to growth in serum-free, selective medium. Duplicate T25cm<sup>2</sup> flasks were set up. Cells from one flask were frozen down as a stock and cells in the second flask were grown to saturation. The productivity of the saturated cultures was assessed by ELISA. The highest producing cell lines were then selected for large-scale antibody production.

**[0760]** The above procedure is exemplified for the I006D08 anti-BLyS antibody constructs. Following electroporation and selection of NS0 cells, supernatants from ninety-three wells each containing a single colony were screened by ELISA to detect assembled IgG1, antibody. Twenty-seven of the supernatants were identified as containing IgG. The colonies from 24 of the positive wells were transferred to 1ml

selective medium in a 24-well plate and allowed to grow for 2 days. The 1ml cultures of cells were then added to 4ml selective medium containing reduced serum (0.5% FCS) in a T25cm<sup>2</sup> flask. When the cultures reached confluency 1 ml cells were diluted in 4ml selective, serum-free medium in a T25cm<sup>2</sup> flask. At confluency this subculture regime was repeated again. Finally 1ml cells from the culture containing 0.1% FCS was diluted with 9 ml serum-free, selective medium and divided into 2 x T25cm<sup>2</sup> to form the saturated and stock cultures. The stock cultures were frozen down and stored in liquid nitrogen once the cultures were confluent. The saturation culture was grown until the viability of the culture was < 10%. Twenty-three out of the 24 colonies originally expanded were successfully adapted to growth in serum-free medium. The productivity of these serum-free adapted cell lines ranged from 0.3 to 17 µg/ml by ELISA quantification of the saturated, 5ml serum-free cultures. The I006D08-32 cell line produced 17 µg/ml.

#### Large-scale IgG production

**[0761]** The highest-producing cell lines were revived from frozen stocks and then expanded to 400ml in selective, serum-free medium in 2 liter roller bottles. The cells were grown at 37 °C and rolled at 4 rpm with the headspace being re-equilibrated with 5% CO<sub>2</sub>/air every 2-3 days. Finally the culture was expanded to a 4 liter volume by the addition of serum-free medium without selection (400 ml per 2 liter roller bottle). The cultures were then grown to saturation.

**[0762]** This procedure is exemplified by the production of I006D08 antibody from the I006D08-32 cell line. The frozen stock of I006D08-32 was revived into a T25 cm<sup>2</sup> containing 5 ml serum-free medium containing 1mg/ml geneticin and grown at 37 °C in 5% CO<sub>2</sub>/air incubator. After two days growth the culture was diluted with 7.5 ml fresh medium and transferred to a T75cm<sup>2</sup> flask. After a further three days in the incubator the cells were transferred to 130 ml selective medium and transferred to a 2 liter roller bottle. After three days growth the cells were diluted with 500 ml selective medium and split into 2 x 2 liter roller bottles. After another 2 days 100 ml fresh selective medium was added to each roller. Finally the next day the culture was expanded to a total volume of 4 liters with non-selective medium and divided into 10 x 2 liter roller bottles. After three days the medium was supplemented with 6mM glutamine. The cells were grown for 17 days from the final subculture into a 4 liter volume. The cells grew up to 3 x10<sup>6</sup> cells/ml before

viability declined to  $< 0.2 \times 10^6$  cells/ml. At this low viability the culture supernatants were harvested. ELISA analysis indicated that the culture supernatant contained 33  $\mu\text{g/ml}$  IgG. Hence, the 4 liter culture contained 132 mg IgG.

### IgG Purification

**[0763]** The purification of the IgG from the fermentation broth is performed using a combination of conventional techniques commonly used for antibody production. Typically the culture harvest is clarified to remove cells and cellular debris prior to starting the purification scheme. This would normally be achieved using either centrifugation or filtration of the harvest. Following clarification, the antibody would typically be captured and significantly purified using affinity chromatography on Protein A Sepharose. The antibody is bound to Protein A Sepharose at basic pH and, following washing of the matrix, is eluted by a reduction of the pH. Further purification of the antibody is then achieved by gel filtration. As well as removing components with different molecular weights from the antibody this step can also be used to buffer exchange into the desired final formulation buffer.

### Purification of I006D08 IgG1

**[0764]** The harvest was clarified by sequential filtration through 0.5  $\mu\text{m}$  and 0.22  $\mu\text{m}$  filters. Clarified harvest was then applied to a column of recombinant Protein A Sepharose equilibrated at pH 8.0 and washed with the equilibration buffer. I006D08 antibody was eluted from the Protein A Sepharose by application of a buffer at pH3.5. The collected antibody containing eluate was then neutralized to pH 7.4 by the addition of pH 8.0 buffer. The neutralized eluate was concentrated by ultrafiltration using a 30 KDa cut off membrane. Concentrated material was then purified by Sephacryl S300HR gel filtration using phosphate buffered saline as the mobile phase. The final monomeric IgG1 fraction from the gel filtration column was then concentrated to the desired formulation concentration by ultrafiltration using a 30 KDa cut off membrane. The final product was filtered through a 0.22  $\mu\text{m}$  filter.

Example 21: Antibody neutralization of murine splenocyte proliferation as measured by 3HdT incorporation

**[0765]** To determine if an antibody inhibited BLyS mediated B cell proliferation, a splenocyte proliferation assay was performed. Briefly, murine splenocytes were isolated by flushing spleen with complete medium using a 25g needle and 10 ml of complete medium (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100µg/ml streptomycin, 4mM glutamine,  $5 \times 10^{-5}$ M  $\beta$ -mercaptoethanol). The cells were passed through a 100 micron nylon filter to remove cell clumps. The cell suspension was then ficolled at 400 x g for 25 minutes at room temperature (one 15 ml conical tube/spleen; 3 ml ficol, 10 ml cell suspension/spleen; Ficoll 1083 from Sigma). The recovered cells were washed 3 times in complete medium and counted. Recovered cells were then diluted to a concentration of  $3 \times 10^6$ /ml in complete medium containing a 3X concentration of SAC (3X = 1:33,333 dilution of stock) (Staph. aureus Cowan strain; Calbiochem).

**[0766]** For each antibody, 50 microliters of antibody dilutions at 30µg/ml, 3.0µg/ml, and 0.3µg/ml concentrations were aliquotted into individual wells of a 96 well plate in triplicate. Suitable positive controls, such as, for example monoclonal antibody 15C10, were also used. Medium containing no antibody (and human isotype controls (purchased commercially) when necessary) were used as negative controls.

**[0767]** BLyS protein was diluted in complete medium to concentrations of 300ng/ml, 90ng/ml and 30ng/ml. 50 microliters of each of the BLyS dilutions were then added to the antibody dilution series in the plates. The plate containing the antibody and BLyS dilutions are then incubated for 30 minutes at 37°C, 5% CO<sub>2</sub>, after which 50 microliters of the splenocyte cell suspension containing SAC was added to all wells. The plates were then incubated for 72 hours (37°C, 5% CO<sub>2</sub>).

**[0768]** After 72 hours, each well was supplemented with 50µl of complete medium containing 0.5µCi of 3H-thymidine (6.7 Ci/mM; Amersham) and cells were incubated for an additional 20-24 hours at (37°C, 5% CO<sub>2</sub>). Following incubation cells were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

Example 22: Human B cell proliferation assay for in vitro screening of BLyS antagonist



molecules

**[0769]** The bioassay for assessing the effects of putative BLyS antagonists was performed in triplicate in 96 well format by mixing equal volumes of BLyS, responder cells, and putative antagonist each of which is prepared as a 3X stock reagent.

**[0770]** B-lymphocytes were purified from human tonsil by MACS (anti-CD3 depletion), washed, and resuspended in complete medium (CM) (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100µg/ml streptomycin, 4mM glutamine, 5x10E-5 M beta-mercaptoethanol) at a concentration of  $3 \times 10^6$  cells/mL. *Staphylococcus aureus*, Cowan I (SAC, CalBiochem) was added to cells at 3X concentration (3X = 1:33,333 dilution of stock

**[0771]** Meanwhile, eight serial dilutions (3-fold) of potential antagonist were prepared in CM such that the diluted antagonists are at 3X the final concentrations to be tested in the assay. Antibodies are routinely tested starting at a final concentration of 10ug/mL and going down to about 1.5 ng/mL.

**[0772]** Human rBLyS was prepared in CM to 3X concentration (3X = 300 ng/mL, 30 ng/mL, and 3 ng/mL) in CM. Potential inhibitors were routinely tested at several concentrations of BLyS to avoid false negatives due to unexpectedly low affinity or antagonist concentration.

**[0773]** Fifty microliters of diluted antagonist and 50uL of diluted BLyS were added to the putative antagonist dilution series.

**[0774]** Cells were then incubated for 72 hours (37°C, 5% CO<sub>2</sub>) in a fully humidified chamber. After 72 hrs., the cells were supplemented with 0.5 µCi/well 3H-thymidine (6.7 Ci/mmol) and incubated for an additional 24 hours. Plates were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

[0775] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in this application is incorporated in their entireties herein by reference. Further, the sequences disclosed herein are also disclosed in U.S. Provisional Application 60/212,210 filed June 16, 2000 the contents of which are incorporated in their entireties herein by reference.

Table 1: scFvs that Immunosepecifically Bind to BlyS

Table 1: scFvs that Immunosepecifically Bind to BlyS

Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VH	AAs of VL CDR1	AAs of VH CDR1	AAs of VL CDR2	AAs of VH CDR2	AAs of VH CDR3	AAs of VH CDR3	Sequence (SEQ ID NO)
1003F12S	1	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	HDDDLVLTGYVFE (SEQ ID NO: 2130)
1006D08	2	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDDLLPFHYGMDV (SEQ ID NO: 2133)
1008A11	3	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	DRYDLTGYYYGMDV (SEQ ID NO: 2129)
1017D10	4	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121	VQMDSEYDILTGINVPFYFDH (SEQ ID NO: 2132)
1022D01	5	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGSYYGMDV (SEQ ID NO: 2135)
1031F02	6	137-251	160-173	189-195	228-240	1-121	26-35	50-66	99-110	GYPDSSAKRAFDI (SEQ ID NO: 2136)
1050A12	7	140-250	164-174	190-196	229-239	1-124	26-35	50-66	99-113	APYDILLTHYHYFDY (SEQ ID NO: 2134)
1051C04	8	145-256	168-181	197-203	236-245	1-129	26-35	50-66	99-118	AATTSQKINKYAYFYGMDV (SEQ ID NO: 2131)
1050B11	9	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1050B11-01	10	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2143)
1050B11-02	11	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2143)
1050B11-03	12	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2143)
1050B11-04	13	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2144)
1050B11-05	14	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2141)
1050B11-06	15	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2142)
1050B11-07	16	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2140)
1050B11-08	17	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2144)
1050B11-09	18	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2141)
1050B11-10	19	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2142)
1050B11-11	20	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2142)
1050B11-12	21	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2140)
1050B11-13	22	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2140)
1050B11-14	23	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1050B11-15	24	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1050B11-16	25	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVWA (SEQ ID NO: 2143)
1050B11-17	26	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2143)
1050B11-18	27	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2144)
1050B11-19	28	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2144)
1050B11-20	29	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2139)

1050B11-21	30	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2138)
1050B11-22	31	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2138)
1050B11-23	32	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2138)
1050B11-24	33	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2139)
1050B11-25	34	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2144)
1050B11-26	35	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2139)
1050B11-27	36	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2138)
1050B11-28	37	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2137)
1093D03	38	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVILGYGLS (SEQ ID NO: 2145)
1093D09	39	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1093G08	40	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYVVA (SEQ ID NO: 2143)
1097D11	41	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2139)
1101A04	42	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1101B01	43	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1102A02	44	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1102E01	45	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2144)
1102G06	46	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTRYVFOYFDH (SEQ ID NO: 2141)
1087A07	47	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVILPRVIP (SEQ ID NO: 2277)
1087A08	48	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVCRPHF (SEQ ID NO: 2238)
1087A09	49	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVRCPPV (SEQ ID NO: 2272)
1087B02	50	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVFRPL (SEQ ID NO: 2281)
1087B03	51	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVKSMT (SEQ ID NO: 2305)
1087B04	52	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPLYC (SEQ ID NO: 2292)
1087B05	53	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVVPST (SEQ ID NO: 2270)
1087B06	54	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVGHGL (SEQ ID NO: 2282)
1087B08	55	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVCPSPR (SEQ ID NO: 2240)
1087B09	56	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVCPYA (SEQ ID NO: 2240)
1087C02	57	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPLLS (SEQ ID NO: 2224)
1087C05	58	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVALYRL (SEQ ID NO: 2234)
1087C06	59	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVRASF (SEQ ID NO: 2271)
1087C07	60	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVTPSP (SEQ ID NO: 2319)
1087C08	61	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVWPSP (SEQ ID NO: 2277)
1087D01	62	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVTPRGY (SEQ ID NO: 2275)
1087D02	63	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVSSLS (SEQ ID NO: 2213)
1087D03	64	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVPLPLC (SEQ ID NO: 2263)
1087D05	65	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVPPPSFL (SEQ ID NO: 2266)

1087D07	66	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPTSTT (SEQ ID NO: 2269)
1087D09	67	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVSCSWA (SEQ ID NO: 2299)
1087E04	68	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVSALPPP (SEQ ID NO: 2274)
1087E05	69	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVCRHLF (SEQ ID NO: 2306)
1087E10	70	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVSPSL (SEQ ID NO: 2307)
1087F02	71	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVMGVTPS (SEQ ID NO: 2322)
1087F04	72	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLRPVL (SEQ ID NO: 2326)
1087F05	73	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPSVGG (SEQ ID NO: 2267)
1087F07	74	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPPTRH (SEQ ID NO: 2286)
1087F08	75	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVLRSD (SEQ ID NO: 2243)
1087F09	76	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPLPP (SEQ ID NO: 2310)
1087G05	77	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVLRCLV (SEQ ID NO: 2239)
1087G06	78	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVHPSRS (SEQ ID NO: 2285)
1087G07	79	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLRPPQ (SEQ ID NO: 2241)
1087G08	80	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVGPYGT (SEQ ID NO: 2284)
1087GH0	81	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVTPCT (SEQ ID NO: 2276)
1087H02	82	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASVLTSSSLDN (SEQ ID NO: 2265)
1088A01	83	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088A03	84	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVIBPLPL (SEQ ID NO: 2290)
1088A04	85	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHIHPH (SEQ ID NO: 2335)
1088A08	86	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFEYYAS (SEQ ID NO: 2323)
1088A09	87	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYLH (SEQ ID NO: 2295)
1088B00	88	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088A11	89	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLMVPPH (SEQ ID NO: 2220)
1088A12	90	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLFYPL (SEQ ID NO: 2325)
1088B01	91	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088B02	92	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFEYYAS (SEQ ID NO: 2244)
1088B03	93	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVIBPLPL (SEQ ID NO: 2290)
1088B05	94	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088B06	95	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFEYYSL (SEQ ID NO: 2324)
1088B07	96	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088B08	97	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088B09	98	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEPYL (SEQ ID NO: 2303)
1088B10	99	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYEDH (SEQ ID NO: 2137)
1088B12	100	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVPLDS (SEQ ID NO: 2223)
1088C01	101	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYFYP (SEQ ID NO: 2317)

102	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088C03	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088C09	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088C12	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088D01	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088D03	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088D04	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088D07	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVLPSPV (SEQ ID NO: 2225)	
1088D08	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088D11	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)	
1088E01	111	138-248	163-174	190-196	229-237	1-122	23-32	47-63	96-111	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088E02	112	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLHYLY (SEQ ID NO: 2216)
1088E03	113	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088E04	114	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088E08	115	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088E10	116	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088E11	117	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088F07	118	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088G02	119	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088G03	120	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088G07	121	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1088G09	122	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2260)
1088G10	123	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2264)
1088H05	124	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLHFIDH (SEQ ID NO: 2301)
1088H07	125	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092A03	126	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092A05	127	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092A06	128	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2258)
1092A08	129	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092A10	130	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2283)
1092A11	131	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092B01	132	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092B02	133	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092B04	134	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092B05	135	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092B10	136	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)
1092B12	137	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFRQYFDH (SEQ ID NO: 2137)

1092C01	138	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092C02	139	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092C07	140	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILTSYVVLADL (SEQ ID NO: 2328)
1092C08	141	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFGYSL (SEQ ID NO: 2134)
1092C12	142	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFKYYTD (SEQ ID NO: 2137)
1092D01	143	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2226)
1092D07	144	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092D09	145	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVNMHAYPL (SEQ ID NO: 2255)
1092D10	146	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHHYLPV (SEQ ID NO: 2256)
1092D11	147	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092E01	148	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092E03	149	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVAFQYFQYFDH (SEQ ID NO: 2230)
1092E04	150	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFEYSV (SEQ ID NO: 2248)
1092E07	151	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092E10	152	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLFYPL (SEQ ID NO: 2327)
1092E11	153	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F01	154	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F02	155	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F05	156	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F07	157	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F08	158	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F11	159	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092F12	160	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLAAYPD (SEQ ID NO: 2306)
1092G01	161	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092G05	162	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092G10	163	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1092H10	164	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093A06	165	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2265)
1093A09	166	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2334)
1093A11	167	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093A12	168	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2268)
1093B02	169	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093B05	170	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093B06	171	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2289)
1093B09	172	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093B12	173	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEVYHP (SEQ ID NO: 2318)
										PFYDILTSYVFAPLVT (SEQ ID NO: 2242)

1093C02	174	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYHAYAF (SEQ ID NO: 2132)
1093C03	175	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093C05	176	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYLH (SEQ ID NO: 2295)
1093D05	177	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFEFLPL (SEQ ID NO: 2245)
1093D08	178	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVRPFAH (SEQ ID NO: 2273)
1093D10	179	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093D12	180	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLFHYRV (SEQ ID NO: 2302)
1093E01	181	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093E02	182	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093E03	183	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2283)
1093E08	184	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHEFTSL (SEQ ID NO: 2297)
1093E10	185	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVMQFPFP (SEQ ID NO: 2321)
1093F01	186	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLSFPVP (SEQ ID NO: 2246)
1093F03	187	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYYYAF (SEQ ID NO: 2251)
1093F05	188	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093F08	189	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093F11	190	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093G07	191	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLFHYPL (SEQ ID NO: 2333)
1093G11	192	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYQYYVL (SEQ ID NO: 2237)
1093G12	193	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1093H06	194	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094A08	195	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094B07	196	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094B08	197	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLPVWVS (SEQ ID NO: 2228)
1094B12	198	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094C11	199	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094C12	200	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094D06	201	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094D07	202	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094D08	203	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2288)
1094D09	204	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094D10	205	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYLHPL (SEQ ID NO: 2314)
1094D11	206	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094E04	207	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFEHPVP (SEQ ID NO: 2218)
1094E08	208	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVQYFQYFDH (SEQ ID NO: 2137)
1094F04	209	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEAFTSL (SEQ ID NO: 2311)
										PFYDILTSYVFGYPFP (SEQ ID NO: 2252)



1094F05	210	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1094F10	211	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2278)
1094F11	212	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVLWYYQD (SEQ ID NO: 2249)
1094F12	213	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVIFPYL (SEQ ID NO: 2296)
1094G06	214	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1094G10	215	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095A04	216	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095A12	217	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEYPPL (SEQ ID NO: 2320)
1095B04	218	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEFFPA (SEQ ID NO: 2312)
1095B09	219	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEPL (SEQ ID NO: 2287)
1095B10	220	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEHYSA (SEQ ID NO: 2317)
1095C02	221	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEHYTA (SEQ ID NO: 2331)
1095C05	222	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEHLPV (SEQ ID NO: 2337)
1095C07	223	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095C08	224	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095C09	225	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVWMHYPT (SEQ ID NO: 2259)
1095D01	226	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095D02	227	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLOXYRY (SEQ ID NO: 2235)
1095D03	228	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLOXYRY (SEQ ID NO: 2235)
1095D05	229	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLOXYRY (SEQ ID NO: 2235)
1095D09	230	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095E01	231	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095E05	232	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLDYSS (SEQ ID NO: 2309)
1095E12	233	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDALTSYVFOYFQYEDH (SEQ ID NO: 2221)
1095F06	234	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095F09	235	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFPYPH (SEQ ID NO: 2262)
1095G06	236	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVIGFPV (SEQ ID NO: 2291)
1095G09	237	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1095G11	238	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVMDFSV (SEQ ID NO: 2253)
1096A01	239	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1096A10	240	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1096B01	241	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLPYAL (SEQ ID NO: 2222)
1096B03	242	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1096C01	243	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1096C06	244	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)
1096C09	245	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLPVLT (SEQ ID NO: 2229)
										PFYDILTSYVFOYFQYEDH (SEQ ID NO: 2137)

1096D01	246	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096D02	247	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096D05	248	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096D06	249	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096D09	250	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096E02	251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096E06	252	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVLGFVPY (SEQ ID NO: 2329)
1096E06	252	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVLHYVTH (SEQ ID NO: 2336)
1096E11	253	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096R02	254	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVIHPLP (SEQ ID NO: 2330)
1096G01	255	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVIFLPL (SEQ ID NO: 2290)
1096G02	256	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096G05	257	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096G07	258	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1096G09	259	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVMHYLPV (SEQ ID NO: 2257)
1096G12	260	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEFSSH (SEQ ID NO: 2315)
1096H01	261	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASYLSTSSLDN (SEQ ID NO: 2265)
1097A04	262	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLVLT (SEQ ID NO: 2294)
1097A06	263	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLPYTL (SEQ ID NO: 2231)
1097A09	264	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLVYPI (SEQ ID NO: 2298)
1097B02	265	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLVYPL (SEQ ID NO: 2247)
1097B09	266	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097B10	267	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097B11	268	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097C05	269	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLHYVTH (SEQ ID NO: 2219)
1097C09	270	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLHYAY (SEQ ID NO: 2316)
1097C11	271	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097D05	272	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVHLFYSL (SEQ ID NO: 2293)
1097D06	273	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFGFPPH (SEQ ID NO: 2300)
1097E01	274	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097E04	275	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097E08	276	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097F09	277	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097G10	278	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)
1097G10	279	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFAH (SEQ ID NO: 2268)
1097H02	280	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASYLSTSSLDN (SEQ ID NO: 2265)
1098A04	281	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVVFQYFDH (SEQ ID NO: 2137)

1098A05	282	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098B08	283	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLDYFSV (SEQ ID NO: 2308)
1098C01	284	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2278)
1098C04	285	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYYYAF (SEQ ID NO: 2251)
1098F01	286	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098F02	287	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFFRPF (SEQ ID NO: 2250)
1098G02	288	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G12	289	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098H05	290	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I01	291	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I04	292	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I06	293	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLEPFD (SEQ ID NO: 2304)
1098I07	294	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I08	295	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I09	296	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I12	297	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I20	298	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I21	299	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G01	300	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G03	301	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G06	302	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G08	303	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G09	304	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVLYYYAH (SEQ ID NO: 2214)
1098A09	305	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098B02	306	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098B06	307	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098C07	308	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098E05	309	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098E12	310	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G01	311	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G03	312	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098B06	313	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098I12	314	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098E12	315	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098G06	316	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)
1098H04	317	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILTSYVFOYFDH (SEQ ID NO: 2137)

1110803	318	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PEYDILTSYVFOYFDH (SEQ ID NO: 2137)
1112D09	319	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PEYDILTSYVFOYFDH (SEQ ID NO: 2232)
1112F10	320	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PEYDILTSYVFOYFDH (SEQ ID NO: 2137)
1089F12	321	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDS (SEQ ID NO: 2146)
1105E12	322	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHFSDL (SEQ ID NO: 2147)
1108D08	323	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHGLDV (SEQ ID NO: 2148)
1108E06	324	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2151)
1113E07	325	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2151)
1114G05	326	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2152)
1116A01	327	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2147)
1116A09	328	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2149)
1116C11	329	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2150)
1085A01	330	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2147)
1085A02	331	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2602)
1085A03	332	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2639)
1085A04	333	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2561)
1085A05	334	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2550)
1085A06	335	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2659)
1085A07	336	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2611)
1085A09	337	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDILLPPHHGLDV (SEQ ID NO: 2390)
1085A10	338	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2632)
1085A11	339	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDILLPPHHGLDV (SEQ ID NO: 2609)
1085B01	340	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2463)
1085B02	341	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2466)
1085B03	342	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2392)
1085B04	343	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2638)
1085B05	344	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2589)
1085B06	345	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2573)
1085B07	346	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2574)
1085B10	347	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDILLPPHHGLDV (SEQ ID NO: 2433)
1085B12	348	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2470)
1085C02	349	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2430)
1085C03	350	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2400)
1085C05	351	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2491)
1085C06	352	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2341)
1085C07	353	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGLDV (SEQ ID NO: 2375)

2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

Cell Line	Corresponding scFv	SEQ ID NO:	ATCC Deposit Number	ATCC Deposit Date
NSO-B11-15	I050B11-15	24	PTA-3238	March 27, 2001
NSO-anti-BLyS-6D08-18	I006D08	2	PTA-3239	March 27, 2001
NSO- anti-BLyS-116A01-60	I116A01	327	PTA-3240	March 27, 2001
IO26C04K	I026C04-K	1563	PTA-3241	March 27, 2001
IO50A12	I050A12	12	PTA-3242	March 27, 2001
IO50B11	I050B11	9	PTA-3243	March 27, 2001

**[0275]** Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

**[0276]** In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11-15.

**[0277]** In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BLyS-6D08-18.

**[0278]** In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO- anti-BLyS-116A01-60.

**[0279]** In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO26C04K.

**[0280]** In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO50A12.

**[0281]** In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11.

**[0282]** In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1,

VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by between 1% and 10% in a competitive inhibition assay. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by between 1% and 10% in a competitive inhibition assay.

**[0283]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 10% and up to 20% in a competitive inhibition assay.

**[0284]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 20% and up to 30% in a competitive inhibition assay.

**[0285]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 30% and up to 40% in a competitive inhibition assay.

**[0286]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 40% and up to 50% in a competitive inhibition assay.

**[0287]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 50% and up to 60% in a competitive inhibition assay.

**[0288]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 60% and up to 70% in a competitive inhibition assay.

**[0289]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 70% and up to 80% in a competitive inhibition assay.

**[0290]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 80% and up to 90% in a competitive inhibition assay.

**[0291]** In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 90% and up to 100% in a competitive inhibition assay.

**[0292]** In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3238 to a BLyS polypeptide.

**[0293]** In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3239 to a BLyS polypeptide.

**[0294]** In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3240 to a BLyS polypeptide.

[0295] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3241 to a BLyS polypeptide.

[0296] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3242 to a BLyS polypeptide.

[0297] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3243 to a BLyS polypeptide.

[0298] For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In a specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention comprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the human scFvs referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally CDRs not derived from the scFvs in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same scFv, or different scFvs referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.



**[0299]** A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a human antibody and a non-human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See *e.g.*, Morrison, Science 229:1202 (1985); Oi *et al.*, BioTechniques 4:214 (1986); Gillies *et al.*, J. Immunol. Methods 125:191-202 (1989); U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (*e.g.*, framework regions from a canine or feline immunoglobulin molecule) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka *et al.*, Protein Engineering 7(6):805-814 (1994); Roguska *et al.*, PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFv disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Patent No. 5,585,089; Riechmann *et al.*, Nature 332:323 (1988), which are incorporated herein by reference in their entirety.)

**[0300]** Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" BLyS polypeptides using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, FASEB J. 7(5):437-444 (1993); and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies of the invention which bind to BLyS and competitively inhibit the binding of BLyS to its

receptor (as determined by assays well known in the art such as, for example, that disclosed, *infra*) can be used to generate anti-idiotypes that “mimic” a BLyS ligand/receptor-binding domain and, as a consequence, bind to and neutralize BLyS receptors (e.g., TACI, BCMA, and TR20). Such neutralizing anti-idiotypes (including molecules comprising, or alternatively consisting of, antibody fragments or variants, such as Fab fragments of such anti-idiotypes) can be used in therapeutic regimens to neutralize BLyS. For example, such anti-idiotypic antibodies can be used to bind BLyS ligands/receptors, and thereby block BLyS mediated biological activity. Alternatively, anti-idiotypes that “mimic” a BLyS binding domain may bind to BLyS receptor(s) and induce BLyS receptor mediated signalling (e.g., activation of nuclear factor of activated T cells (NF-AT), nuclear factor-kappa B (NF-kappa B), and/or AP-1). Such agonistic anti-idiotypes (including agonistic Fab fragments of these anti-idiotypes) can be used in therapeutic regimens to induce or enhance BLyS receptor mediated signalling. For example, such anti-idiotypic antibodies can be used to bind BLyS ligands/receptors, and thereby stimulate BLyS mediated biological activity (e.g., B cell proliferation and/or immunoglobulin production).

**[0301]** Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule, such as, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

#### Polynucleotides Encoding an Antibody

**[0302]** The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). The invention also encompasses polynucleotides that hybridize under high

stringency, or alternatively, under intermediate or lower stringency hybridization conditions, *e.g.*, as defined *supra*, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

**[0303]** The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the scFv antibodies and VH domains, VL domains and CDRs thereof, are known (as described in Table 1), nucleotide sequences encoding these antibodies can be determined using methods well known in the art, *i.e.*, the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier *et al.*, BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

**[0304]** Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

**[0305]** Once the nucleotide sequence of the antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods

well known in the art for the manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel *et al.*, eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entirety), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

**[0306]** In a specific embodiment, one or more of the VH and VL domains referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, *e.g.*, Chothia *et al.*, J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to BLyS. Preferably, as discussed *supra*, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

#### Recombinant Expression of an Antibody

**[0307]** Recombinant expression of an antibody of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or

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**[0308]** The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

**[0309]** A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include, but are not limited to, microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking *et al.*, Gene 45:101 (1986); Cockett *et al.*, Bio/Technology 8:2 (1990)).

**[0310]** In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, EMBO 1. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a

fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

**[0311]** In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

**[0312]** In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region EI or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, *e.g.*, Bittner *et al.*, Methods in Enzymol. 153:51-544 (1987)).

**[0313]** In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*,

cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERY, BHK, HeLa, COS, NSO, MDCK, 293, 3T3, W138, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT2O and T47D, and normal mammary gland cell line such as, for example, CRL703O and HsS78Bst.

**[0314]** For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

**[0315]** A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, Cell 11:223 (1977)), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy *et al.*, Cell 22:8 17 (1980)) genes can be employed in tk-, hgprt- or apt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler *et al.*, Natl. Acad. Sci. USA 77:357 (1980); O'Hare *et al.*, Proc. Natl. Acad. Sci. USA 78:1527 (1981)); *gpt*, which confers



resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62: 191-217 (1993); TIB TECH 11(5):155-2 15 (May, 1993)); and *hygro*, which confers resistance to hygromycin (Santerre *et al.*, Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin *et al.*, J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

**[0316]** The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse *et al.*, Mol. Cell. Biol. 3:257 (1983)).

**[0317]** The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

**[0318]** Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for

purification of an immunoglobulin molecule, or more generally, for purification of a protein, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

#### Antibody Characterization

**[0319]** Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to immunospecifically bind to BLyS or a fragment of BLyS (*e.g.*, to the soluble form or the membrane-bound form of BLyS) using techniques described herein or routinely modifying techniques known in the art. BLyS or BLyS fragments that may be immunospecifically bound by the compositions of the invention include, but are not limited to, human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (*e.g.*, the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes) or fragments thereof. Preferably compositions of the invention bind human BLyS (SEQ ID NOS:3228 and/or 3229) or fragments thereof. Assays for the ability of the antibodies of the invention to immunospecifically bind BLyS or a fragment of BLyS may be performed in solution (*e.g.*, Houghten, *Bio/Techniques* 13:412-421(1992)), on beads (*e.g.*, Lam, *Nature* 354:82-84 (1991)), on chips (*e.g.*, Fodor, *Nature* 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., *Proc. Natl. Acad. Sci. USA* 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, *Science* 249:386-390 (1990); Devlin, *Science* 249:404-406 (1990); Cwirla et al., *Proc. Natl. Acad. Sci. USA* 87:6378-6382 (1990); and Felici, *J. Mol. Biol.* 222:301-310 (1991)) (each of

these references is incorporated herein in its entirety by reference). Antibodies that have been identified to immunospecifically bind to BLyS or a fragment of BLyS can then be assayed for their specificity and affinity for BLyS or a fragment of BLyS using or routinely modifying techniques described herein or otherwise known in the art.

**[0320]** The antibodies of the invention may be assayed for immunospecific binding to BLyS and cross-reactivity with other antigens by any method known in the art. In particular, the ability of an antibody to immunospecifically bind to the soluble form or membrane-bound form of BLyS and the specificity of the antibody, fragment, or variant for BLyS polypeptide from a particular species (e.g., murine, monkey or human, preferably human) may be determined using or routinely modifying techniques described herein or otherwise known in art .

**[0321]** Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

**[0322]** Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as

to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

**[0323]** Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

**[0324]** ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as

an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

**[0325]** The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for BLyS and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, BLyS is incubated with an antibody of the present invention conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second anti-BLyS antibody.

**[0326]** In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to BLyS, or fragments of BLyS. BIAcore kinetic analysis comprises analyzing the binding and dissociation of BLyS from chips with immobilized antibodies on their surface as described in detail in Examples 6, 12, 17 and 18, *infra*.

**[0327]** The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can also be assayed for their ability to inhibit, increase, or not significantly alter, the binding of BLyS to a BLyS receptor (e.g., TACI and BCMA) using techniques known to those of skill in the art. For example, cells expressing a receptor for BLyS (e.g., IM9, REH, ARH-77 cells, Namalwa, and RPMI-8226 B cell tumor lines as well as peripheral CD20+ B cells) can be contacted with BLyS in the presence or absence of an antibody, and the ability of the antibody to inhibit, increase, or not significantly alter, BLyS binding to the cells can be measured. BLyS binding to cells can be measured by, for example, flow

cytometry or a scintillation assay. BLyS or the antibody can be labeled with a detectable compound such as a radioactive label (e.g.,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , and  $^{125}\text{I}$ ) or a fluorescent label (e.g., fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine) to enable detection of an interaction between BLyS and a BLyS receptor and/or BLyS and an antibody of the invention. Alternatively, the ability of antibodies of the invention to inhibit, increase, or not significantly alter, BLyS binding to a BLyS receptor can be determined in cell-free assays. For example, native or recombinant BLyS (e.g., that having the amino acid sequence of amino acids 134 – 285 of SEQ ID NO:3228) or a fragment thereof can be contacted with an antibody and the ability of the antibody to inhibit, increase, or not significantly alter, BLyS from binding to a BLyS receptor can be determined. Preferably, the antibody is immobilized on a solid support and BLyS or a BLyS fragment is labeled with a detectable compound. Alternatively, BLyS or a BLyS fragment is immobilized on a solid support and the antibody is labeled with a detectable compound. BLyS may be partially or completely purified (e.g., partially or completely free of other polypeptides) or part of a cell lysate. Further, the BLyS polypeptide may be a fusion protein comprising BLyS or a biologically active portion thereof and a domain such as an Immunoglobulin Fc or glutathionine-S-transferase. For example, amino acid residues 1-154 of TACI (GenBank accession number AAC51790), or 1-48 of BCMA (GenBank accession number NP\_001183) may be fused to the Fc region of an IgG molecule and used in a cell free assay to determine the ability of antibodies of the invention to inhibit, increase, or not significantly alter, BLyS binding to a BLyS receptor. Alternatively, BLyS can be biotinylated using techniques well known to those of skill in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, IL).

**[0328]** The antibodies of the invention (including scFvs or other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can also be assayed for their ability to inhibit, stimulate, or not significantly alter, BLyS-induced B-cell proliferation using techniques known to those of skill in the art. For example, B-cell proliferation can be assayed by  $^3\text{H}$ -thymidine incorporation assays and trypan blue cell counts (see, e.g., Moore *et al.*, Science 285: 260-263 (1999)). Further, the antibodies of the invention, or fragments or variants thereof, can be assayed for their ability to block, stimulate, or not significantly alter, BLyS-induced activation of cellular signaling

molecules and transcription factors such as calcium-modulator and cyclophilin ligand ("CAML"), calcineurin, nuclear factor of activated T cells transcription factor ("NF-AT"), nuclear factor-kappa B ("NF-kappa B"), and AP-1 using techniques known to those of skill in the art (see, e.g., von Bulow and Bram, Science 278:138-141(1997)). For example, NF-AT activity can be determined by electromobility gel shift assays, by detecting the expression of a protein known to be regulated by NF-AT (e.g., IL-2 expression), by detecting the induction of a reporter gene (e.g., an NF-AT regulatory element operably linked to a nucleic acid encoding a detectable marker such as luciferase, beta-galactosidase or chloramphenicol acetyltransferase (CAT)), or by detecting a cellular response (e.g., cellular differentiation, or cell proliferation).

**[0329]** The antibodies of the invention, or fragments or variants thereof can also be assayed for their ability to neutralize, enhance, or not significantly alter, BLyS activity. For example, antibodies or fragments or variants thereof, may be routinely tested for their ability to inhibit BLyS from binding to cells expressing the receptor for BLyS (see Example 3, *infra*).

#### Selection and Screening for Antibodies that Immunospecifically Bind to Soluble BLyS

**[0330]** Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the soluble form of BLyS. In one particular assay, antibodies that bind to the biotinylated soluble form of BLyS in solution are captured on streptavidin coated magnetic beads. This assay may be relatively applied to identify antibodies of the invention that neutralize and/or bind to BLyS. Additionally, antibodies may be assayed in neutralization assays described herein or otherwise known in the art (see Example 3, *infra*). For example, antibodies may be tested for their ability to inhibit soluble BLyS (e.g., biotinylated BLyS) from binding to IM9 cells. In this assay, labeled soluble BLyS (e.g., biotinylated BLyS) is incubated with candidate anti-BLyS antibodies to allow for the formation of BLyS-anti-BLyS antibody complexes. Following incubation, an aliquot of the BLyS-anti-BLyS antibody sample is added to IM9 cells. The binding of soluble BLyS may be determined using techniques known in the art. For example, the binding of biotinylated BLyS to IM9 cells may be detected using a fluorimeter following the addition of streptavidin-delfia.

Biotinylated BLyS, if it is not bound by antibodies that neutralize BLyS, binds to the cells is detected. Thus, an antibody that decreases the amount of bio-BLyS that binds to IM-9 cells (relative to a control sample in which the BLyS had been preincubated with an irrelevant antibody or no antibody at all) is identified as one that binds to and neutralizes the soluble form of BLyS. In another assay, antibodies are screened using ELISAs for those antibodies that bind to biotinylated soluble BLyS, but do not bind membrane-bound BLyS, such as, for example, BLyS on membranes from U937 cells (see Examples 2 and 9, *infra*). In these assays, soluble BLyS (e.g., biotinylated BLyS) and membrane-bound BLyS (e.g., on U937 membranes) are incubated in separate samples with the same antibodies and those antibodies that bind to the soluble BLyS (biotinylated BLyS), but not membrane-bound BLyS (e.g., on U937 membranes) are captured and identified.

[0331] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be tested to identify those antibodies that do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (see Example 4, *infra*). Antibodies may also be tested for their affinity for BLyS using, for example, BIAcore analysis (see Examples 6, 12, 17 and 18 *infra*). Antibodies may also be tested for their ability to stimulate, inhibit, or not alter, BLyS-induced immunoglobulin production and/or B-cell proliferation using techniques known to those of skill in the art. For example, human B-cells, BLyS and antibodies may be incubated together in 96 well plates and <sup>3</sup>H-thymidine incorporation may be measured using a scintillation counter.

Selection and Screening for Antibodies that Immunospecifically Bind to Membrane-bound BLyS

[0332] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the membrane-bound form of BLyS. In one particular assay, antibodies that bind to BLyS on U937 membranes or immobilized histidine-tagged BLyS are captured. Other cell lines that express BLyS that might be useful for testing antibody binding to membrane-bound form of BLyS include, K-562, HL-60 and THP-1 cells. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that bind



1086D07	426	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLPPHHTLTF (SEQ ID NO: 2465)
1086D08	427	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLPHSSLDLF (SEQ ID NO: 2473)
1086D09	428	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPNHPMP (SEQ ID NO: 2465)
1086D10	429	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLPPLSSLF (SEQ ID NO: 2387)
1086D11	430	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPNAPLHP (SEQ ID NO: 2610)
1086D12	431	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPRAHLRF (SEQ ID NO: 2469)
1086E02	432	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYDPLHF (SEQ ID NO: 2621)
1086E03	433	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHDALQS (SEQ ID NO: 2598)
1086E05	434	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPRTPLTF (SEQ ID NO: 2367)
1086E07	435	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLHSF (SEQ ID NO: 2398)
1086E08	436	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLTF (SEQ ID NO: 2490)
1086E09	437	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPPLAP (SEQ ID NO: 2464)
1086E10	438	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLDF (SEQ ID NO: 2367)
1086E12	439	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPTAPLRF (SEQ ID NO: 2522)
1086F02	440	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSSPLRT (SEQ ID NO: 2714)
1086F05	441	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPTEPLQF (SEQ ID NO: 2540)
1086F08	442	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPDLSA (SEQ ID NO: 2643)
1086F09	443	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYNPPIF (SEQ ID NO: 2653)
1086F11	444	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHTPLLF (SEQ ID NO: 2489)
1086G03	445	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPDLD (SEQ ID NO: 2513)
1086G04	446	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDPLLT (SEQ ID NO: 2454)
1086G05	447	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDPLRI (SEQ ID NO: 2537)
1086G06	448	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLTP (SEQ ID NO: 2407)
1086G07	449	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDPLLF (SEQ ID NO: 2448)
1086G09	450	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLHSF (SEQ ID NO: 2385)
1086G10	451	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPADLSLF (SEQ ID NO: 2391)
1086G11	452	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPPLTH (SEQ ID NO: 2679)
1089A01	453	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLFPDPLLI (SEQ ID NO: 2612)
1089A03	454	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHTPLHF (SEQ ID NO: 2590)
1089A06	455	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHTPLTF (SEQ ID NO: 2485)
1089A07	456	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDPLTF (SEQ ID NO: 2539)
1089A08	457	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYTPLF (SEQ ID NO: 2682)
1089A10	458	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDPLTF (SEQ ID NO: 2436)
1089A11	459	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPRTYLDLF (SEQ ID NO: 2572)
1089B01	460	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPPLHS (SEQ ID NO: 2450)
1089B02	461	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDPLHFDL (SEQ ID NO: 2147)

1089B03	462	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPTSPLOP (SEQ ID NO: 2528)
1089B04	463	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPTHPLF (SEQ ID NO: 2556)
1089B05	464	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSSPLF (SEQ ID NO: 2712)
1089B06	465	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSSPLF (SEQ ID NO: 2712)
1089B07	466	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLSP (SEQ ID NO: 2596)
1089B08	467	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPYGLDA (SEQ ID NO: 2374)
1089B09	468	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLSP (SEQ ID NO: 2405)
1089B10	469	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPKSPILF (SEQ ID NO: 2384)
1089B11	470	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFTSPILF (SEQ ID NO: 2371)
1089B01	471	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPNSPLF (SEQ ID NO: 2388)
1089C02	472	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHYGMDV (SEQ ID NO: 2133)
1089C03	473	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPILF (SEQ ID NO: 2551)
1089C05	474	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPTHPLF (SEQ ID NO: 2532)
1089C06	475	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSSALRF (SEQ ID NO: 2722)
1089C07	476	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPILF (SEQ ID NO: 2701)
1089C09	477	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQAPLFD (SEQ ID NO: 2683)
1089D01	478	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPFTT (SEQ ID NO: 2507)
1089D02	479	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLVL (SEQ ID NO: 2581)
1089D03	480	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHYGMDV (SEQ ID NO: 2133)
1089D04	481	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPTHPLF (SEQ ID NO: 2344)
1089D05	482	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSSPLF (SEQ ID NO: 2717)
1089D07	483	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLFT (SEQ ID NO: 2546)
1089D08	484	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-112	SRDILLFPNDPLT (SEQ ID NO: 2634)
1089D09	485	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-111	SRDILLFPAPLQ (SEQ ID NO: 2554)
1089D11	486	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSEAPHE (SEQ ID NO: 2677)
1089E01	487	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPNHPLYP (SEQ ID NO: 2663)
1089E02	488	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPILF (SEQ ID NO: 2657)
1089E03	489	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQPLHP (SEQ ID NO: 2346)
1089E04	490	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDAPLFP (SEQ ID NO: 2423)
1089E06	491	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPILT (SEQ ID NO: 2453)
1089E09	492	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSSPLF (SEQ ID NO: 2491)
1089E10	493	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPILT (SEQ ID NO: 2718)
1089E11	494	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQPLSF (SEQ ID NO: 2566)
1089F01	495	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPILWP (SEQ ID NO: 2578)
1089F03	496	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPTEPLLF (SEQ ID NO: 2380)
1089F04	497	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLLL (SEQ ID NO: 2380)
										SRDILLFPSPILF (SEQ ID NO: 2670)

1089FD5	498	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPUR (SEQ ID NO: 2459)
1089FD6	499	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLIF (SEQ ID NO: 2490)
1089FD8	500	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPRTPLTF (SEQ ID NO: 2567)
1089FD9	501	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLIF (SEQ ID NO: 2555)
1089FD10	502	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQPLSF (SEQ ID NO: 2667)
1089FD11	503	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPLEPMHF (SEQ ID NO: 2565)
1089GD01	504	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPAPLTF (SEQ ID NO: 2626)
1089GD02	505	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPHPLF (SEQ ID NO: 2621)
1089GD05	506	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPRTPLVF (SEQ ID NO: 2781)
1089GD06	507	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPPLTF (SEQ ID NO: 2671)
1089GD06	508	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPPLTF (SEQ ID NO: 2389)
1089GD07	509	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLIF (SEQ ID NO: 2514)
1089GD08	510	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPAPLDF (SEQ ID NO: 2597)
1089GD11	511	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPHPLF (SEQ ID NO: 2688)
1089HD10	512	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYVDILTGSYVGMDF (SEQ ID NO: 2135)
1090A02	513	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPPLTF (SEQ ID NO: 2671)
1090A03	514	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLIF (SEQ ID NO: 2416)
1090A04	515	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPNSTLSF (SEQ ID NO: 2678)
1090A05	516	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDAPLTF (SEQ ID NO: 2426)
1090A06	517	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHEPLL (SEQ ID NO: 2648)
1090A07	518	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPYPLSF (SEQ ID NO: 2600)
1090A08	519	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPTEPLVL (SEQ ID NO: 2479)
1090B01	520	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPYPLHF (SEQ ID NO: 2584)
1090B03	521	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLTF (SEQ ID NO: 2627)
1090B04	522	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQAPLTF (SEQ ID NO: 2705)
1090B05	523	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQPLSF (SEQ ID NO: 2452)
1090B06	524	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLHF (SEQ ID NO: 2520)
1090B08	525	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLIF (SEQ ID NO: 2442)
1090B11	526	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQPLRF (SEQ ID NO: 2496)
1090B12	527	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPRTPLTF (SEQ ID NO: 2542)
1090C01	528	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQPLSF (SEQ ID NO: 2474)
1090C02	529	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLIF (SEQ ID NO: 2591)
1090C03	530	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQAPLTF (SEQ ID NO: 2702)
1090C05	531	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLRF (SEQ ID NO: 2493)
1090C06	532	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPRTPLTF (SEQ ID NO: 2567)
1090C07	533	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLDF (SEQ ID NO: 2538)
										SRDILLFPHAGFDS (SEQ ID NO: 2498)

1090C08	534	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPYPLSF (SEQ ID NO: 2676)
1090C10	535	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPGRPLTF (SEQ ID NO: 2358)
1090D02	536	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAHLHF (SEQ ID NO: 2408)
1090D03	537	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPTAPLHP (SEQ ID NO: 2351)
1090D04	538	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHEPLTA (SEQ ID NO: 2654)
1090D05	539	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLPE (SEQ ID NO: 2529)
1090D06	540	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLDF (SEQ ID NO: 2367)
1090D07	541	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPFGTLRF (SEQ ID NO: 2462)
1090D08	542	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLAF (SEQ ID NO: 2505)
1090D09	543	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPLSF (SEQ ID NO: 2579)
1090D12	544	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLPL (SEQ ID NO: 2552)
1090E05	545	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPISF (SEQ ID NO: 2588)
1090E06	546	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQGLSF (SEQ ID NO: 2443)
1090E07	548	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPGLHP (SEQ ID NO: 2484)
1090E09	549	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLSF (SEQ ID NO: 2647)
1090E11	550	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDGLAP (SEQ ID NO: 2700)
1090E12	551	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPTSPLTF (SEQ ID NO: 2582)
1090F01	552	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPNGLHP (SEQ ID NO: 2649)
1090F02	553	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPQAPLSF (SEQ ID NO: 2696)
1090F03	554	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLSF (SEQ ID NO: 2526)
1090F04	555	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLHF (SEQ ID NO: 2359)
1090F05	556	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSEPLQL (SEQ ID NO: 2666)
1090F06	557	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLRF (SEQ ID NO: 2451)
1090F07	558	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPLEPLHF (SEQ ID NO: 2570)
1090F08	559	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPYPLTF (SEQ ID NO: 2344)
1090F09	560	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLRI (SEQ ID NO: 2527)
1090F10	561	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPSPNPLTF (SEQ ID NO: 2698)
1090F11	562	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLEI (SEQ ID NO: 2347)
1090G01	563	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLQF (SEQ ID NO: 2395)
1090G02	564	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHEPLAF (SEQ ID NO: 2653)
1090G04	565	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPAPLAF (SEQ ID NO: 2472)
1090G05	566	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPYPLAF (SEQ ID NO: 2656)
1090G06	567	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPDPLDS (SEQ ID NO: 2480)
1090G07	568	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHTPLTF (SEQ ID NO: 2492)
1090G08	569	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	

1090G09	570	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSEPLRI (SEQ ID NO: 2356)
1090G10	571	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPTAPLDF (SEQ ID NO: 2343)
1090G11	572	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPNGLDF (SEQ ID NO: 2669)
1091A02	573	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYDPLFM (SEQ ID NO: 2724)
1091A03	574	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHPALYP (SEQ ID NO: 2592)
1091A06	575	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPALF (SEQ ID NO: 2594)
1091A11	576	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPITF (SEQ ID NO: 2441)
1091B01	577	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPITF (SEQ ID NO: 2361)
1091B02	578	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091B04	579	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091B05	580	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091B07	581	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091B10	582	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091B11	583	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091B12	584	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C02	585	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C03	586	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C04	587	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C05	588	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C06	589	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C09	590	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C11	591	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091C12	592	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091D01	593	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091D02	594	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091D04	595	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091D05	596	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091D06	597	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLFPYAPLDF (SEQ ID NO: 2606)
1091D07	598	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2456)
1091D09	599	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2645)
1091E01	600	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2719)
1091E02	601	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2425)
1091E03	602	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2689)
1091E04	603	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2352)
1091E06	604	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2576)
1091E07	605	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2661)

1091E08	606	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPNAPLDS (SEQ ID NO: 2607)
1091E09	607	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLDF (SEQ ID NO: 2361)
1091E10	608	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPSSPLFF (SEQ ID NO: 2711)
1091F01	609	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPAPLFF (SEQ ID NO: 2486)
1091F03	610	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPMAPIVG (SEQ ID NO: 2599)
1091F05	611	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPAPLHP (SEQ ID NO: 2553)
1091F06	612	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPHPDPLGF (SEQ ID NO: 2353)
1091F07	613	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPQSPILFF (SEQ ID NO: 2133)
1091F08	614	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPHEHLSF (SEQ ID NO: 2458)
1091F09	615	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPSPILDF (SEQ ID NO: 2354)
1091F10	616	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPSPSLP (SEQ ID NO: 2444)
1091F11	617	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPHYGMDY (SEQ ID NO: 2549)
1091F12	618	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPYAAALYP (SEQ ID NO: 2133)
1091G01	619	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLDF (SEQ ID NO: 2386)
1091G04	620	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNDPLFG (SEQ ID NO: 2355)
1091G05	621	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPQAPLSP (SEQ ID NO: 2478)
1091G06	622	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLDF (SEQ ID NO: 2478)
1091G07	623	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-112	SRDMLFPNAPLDF (SEQ ID NO: 2397)
1091G09	624	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNDPLR (SEQ ID NO: 2637)
1091G10	625	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLDF (SEQ ID NO: 2345)
1091G11	626	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLDF (SEQ ID NO: 2349)
1091G12	627	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNDPLVF (SEQ ID NO: 2660)
1104A01	628	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPQSPILFF (SEQ ID NO: 2389)
1104A07	629	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPYSHLEF (SEQ ID NO: 2655)
1104A08	630	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPQSPILHP (SEQ ID NO: 2455)
1104A09	631	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPQAPLFF (SEQ ID NO: 2689)
1104A10	632	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPYAPLTF (SEQ ID NO: 2617)
1104A11	633	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPQNPILHP (SEQ ID NO: 2506)
1104A12	634	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLDF (SEQ ID NO: 2636)
1104B02	635	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPSPILFF (SEQ ID NO: 2611)
1104B04	636	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2593)
1104B09	637	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2557)
1104B11	638	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2387)
1104C01	639	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2395)
1104C04	640	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2531)
1104C04	641	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2710)
1104C04	641	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDMLFPNAPLRF (SEQ ID NO: 2417)

1104C05	642	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPRHPLLF (SEQ ID NO: 2543)
1104C06	643	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDILLFPHAPLE (SEQ ID NO: 2524)
1104C07	644	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2370)
1104C11	645	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHPEPLF (SEQ ID NO: 2399)
1104C11	646	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHPEPLF (SEQ ID NO: 2644)
1104D01	647	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2652)
1104D02	648	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2483)
1104D03	649	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2511)
1104D04	650	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2491)
1104D07	651	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2595)
1104D08	652	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2500)
1104D09	653	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2502)
1104E01	654	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2447)
1104E02	655	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2641)
1104E03	656	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2463)
1104E05	657	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2385)
1104E11	658	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2364)
1104E12	659	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2616)
1104F02	660	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2481)
1104F03	661	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2402)
1104F04	662	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2573)
1104F05	663	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2465)
1104F06	664	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2362)
1104F07	665	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2544)
1104F10	666	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2559)
1104F11	667	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2476)
1104F12	668	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2518)
1104G04	669	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2482)
1104G05	670	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2494)
1104G09	671	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2147)
1104G11	672	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2487)
1105A02	673	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2378)
1105A03	674	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2557)
1105A04	675	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2557)
1105A08	676	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2557)
1105A09	677	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPHAPLHP (SEQ ID NO: 2557)





1107A07	714	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNAPLSP (SEQ ID NO: 2371)
1107A09	715	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSP (SEQ ID NO: 2699)
1107A12	716	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSF (SEQ ID NO: 2564)
1107B02	717	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLFP (SEQ ID NO: 2553)
1107B04	718	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASPLTF (SEQ ID NO: 2420)
1107B05	719	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYGMV (SEQ ID NO: 21133)
1107C01	720	137-247	161-171	187-193	226-236	1-121	24-33	48-64	97-110	SRDLLLLFPYPLLF (SEQ ID NO: 2344)
1107C04	721	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYPLMF (SEQ ID NO: 2504)
1107C06	722	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYPLMF (SEQ ID NO: 2357)
1107C08	723	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2510)
1107C10	724	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2681)
1107D01	725	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHADF (SEQ ID NO: 2674)
1107D04	726	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYAPLDF (SEQ ID NO: 2361)
1107D07	727	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSP (SEQ ID NO: 2625)
1107D12	728	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2693)
1107D12	729	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2625)
1107E01	730	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2424)
1107E05	731	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2499)
1107E07	732	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLDF (SEQ ID NO: 2367)
1107E09	733	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLDF (SEQ ID NO: 2351)
1107F01	734	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLTF (SEQ ID NO: 2382)
1107F05	735	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSP (SEQ ID NO: 2623)
1107F09	736	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2510)
1107F10	737	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2374)
1107G01	738	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2371)
1107G05	739	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2387)
1107H02	740	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2394)
1107H06	741	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2371)
1107H09	742	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2147)
1107H10	743	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSP (SEQ ID NO: 2496)
1108A12	744	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYPLMF (SEQ ID NO: 2536)
1108B03	745	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2510)
1108B04	746	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2147)
1108C09	747	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSP (SEQ ID NO: 2515)
1108C11	748	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLSP (SEQ ID NO: 2396)
1108D10	749	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASHDF (SEQ ID NO: 2353)
										SRDLLLLFPASHDF (SEQ ID NO: 2429)
										SRDLLLLFPAPLSP (SEQ ID NO: 2364)

I108D11	750	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPASPLNP (SEQ ID NO: 2364)
I108D12	751	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPASPLNP (SEQ ID NO: 2709)
I108E01	752	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E03	753	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E05	754	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E07	755	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E08	756	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E09	757	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E10	758	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E11	759	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108E12	760	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108F01	761	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108G01	762	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108G02	763	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108G07	764	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108G10	765	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108G11	766	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108G12	767	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108H01	768	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108H02	769	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108H06	770	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I108H08	771	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11A06	772	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11B12	773	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I111C01	774	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11D06	775	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11E04	776	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11E10	777	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11E11	778	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11E12	779	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11F07	780	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11G02	781	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11H10	782	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11A04	783	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11A12	784	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)
I11B06	785	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPKHSHFDL (SEQ ID NO: 2147)

113C06	786	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGFD	(SEQ ID NO: 2406)
113G04	787	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF	(SEQ ID NO: 2344)
113G05	788	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYSLLL	(SEQ ID NO: 2344)
113G10	789	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPLQF	(SEQ ID NO: 2517)
113G11	790	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF	(SEQ ID NO: 2413)
113H06	791	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF	(SEQ ID NO: 2344)
113H07	792	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
113H09	793	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
114C04	794	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2344)
114C12	795	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYTLLF	(SEQ ID NO: 2525)
114D04	796	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHGFD	(SEQ ID NO: 2406)
114D06	797	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPQAPLHP	(SEQ ID NO: 2691)
114D10	798	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYGMDV	(SEQ ID NO: 2133)
114E01	799	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
114E02	800	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYSLVL	(SEQ ID NO: 2521)
114E03	801	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPQPLSP	(SEQ ID NO: 2435)
114E11	802	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPQESFL	(SEQ ID NO: 2437)
114H01	803	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPKAPLTF	(SEQ ID NO: 2382)
114H06	804	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2383)
114H09	805	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
115A02	806	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHIALDV	(SEQ ID NO: 2404)
115A07	807	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
115B10	808	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2684)
115C05	809	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF	(SEQ ID NO: 2344)
115C06	810	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
115C08	811	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPAPLVP	(SEQ ID NO: 2501)
115C12	812	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
115D07	813	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2150)
115E09	814	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2424)
115F06	815	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2147)
115H07	816	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2344)
115H12	817	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2148)
115H04	818	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYGMDV	(SEQ ID NO: 2685)
115G04	819	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF	(SEQ ID NO: 2686)
115G05	819	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2150)
115G08	820	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2148)
115H04	821	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF	(SEQ ID NO: 2344)
115H04	821	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHPSFDL	(SEQ ID NO: 2693)
115H04	821	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHIANP	(SEQ ID NO: 2501)

1115H07	822	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF (SEQ ID NO: 2344)
1115H09	823	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHRFDL (SEQ ID NO: 2418)
1116A07	824	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPYPLRF (SEQ ID NO: 2642)
1116B01	825	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2147)
1116B12	826	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2147)
1116C06	827	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF (SEQ ID NO: 2344)
1116D07	828	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2147)
1116E02	829	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2418)
1116E04	830	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2147)
1116F02	831	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2418)
1116F11	832	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2147)
1116G05	833	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLPPHHSFDL (SEQ ID NO: 2150)
1001C09	834	143-250	164-174	190-196	229-239	1-123	26-35	50-66	99-112	SRDILLPPHYPLLF (SEQ ID NO: 2344)
1006D07	835	141-248	162-172	188-194	227-237	1-127	26-35	50-66	99-112	SRDILLPPQAPLSP (SEQ ID NO: 2699)
1007B03	836	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	DGSYDILTYGYYNDMVD (SEQ ID NO: 2154)
1007F11	837	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-116	SHYDILTGLNWWYFDL (SEQ ID NO: 2166)
1007H08	838	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-113	DGSYDILTYGYYNDMVD (SEQ ID NO: 2154)
1008A09	839	146-256	168-181	197-203	236-245	1-130	26-37	52-69	102-117	DGIDILLVPAALMDV (SEQ ID NO: 2160)
1008B01	840	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-119	DRYDILTYGYYGMDV (SEQ ID NO: 2129)
1008C02	841	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-114	DREAYDILTYGYYLYYMDV (SEQ ID NO: 2172)
1008C12	842	143-250	164-174	190-196	229-239	1-127	26-37	52-67	100-118	ATYDPLTGYSDGFDL (SEQ ID NO: 2153)
1008C12	843	146-256	168-181	197-203	236-245	1-130	26-35	50-65	98-116	HVRDYDILTYGRGHYFDY (SEQ ID NO: 2167)
1012A06	844	145-254	169-179	195-201	234-243	1-129	26-37	52-67	100-119	EGSYDILTYGYYGVGRMDV (SEQ ID NO: 2171)
1016E05	845	141-251	163-176	192-198	231-240	1-125	26-37	52-67	100-118	FNPTYDILTYGYYGFFOH (SEQ ID NO: 2155)
1016F02	846	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-114	GRWDYDILTGEHLGYFFDY (SEQ ID NO: 2162)
1016F04	847	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-108	ATYDPLTGYSDGFDL (SEQ ID NO: 2153)
1016H07	848	141-248	162-175	188-194	227-237	1-125	26-35	50-66	99-114	GMGDHYGMDV (SEQ ID NO: 2161)
1018C02	849	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDL (SEQ ID NO: 2153)
1018D07	850	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-114	GYHDLPTSYNNWFDP (SEQ ID NO: 2163)
1018H08	851	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-114	ATYDPLTGYSDGFDL (SEQ ID NO: 2153)
1018H08	852	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DGSYDILTYGYYNDMVD (SEQ ID NO: 2154)
1021B05	853	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DGSYDILTYGYYNDMVD (SEQ ID NO: 2154)
1022E02	854	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	ATYDPLTGYSDGFDL (SEQ ID NO: 2153)
1022E02	855	141-251	163-176	192-198	231-240	1-125	26-35	50-66	97-116	EGNVDYDILTYGYYGAFDI (SEQ ID NO: 2153)
1026E03	856	141-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDL (SEQ ID NO: 2157)
1027A07	857	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	TYDILTYGYPMGYFDY (SEQ ID NO: 2173)
										GGEYDILTYGYYFLGVYDY (SEQ ID NO: 2170)

1028A06	858	142-253	164-176	192-198	231-242	1-126	26-35	50-66	99-115	GGDYDLTGLYYYGMDV (SEQ ID NO: 2156)
1029D07	859	141-250	163-176	192-198	231-239	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1029F11	860	143-253	165-177	192-199	232-242	1-127	26-35	50-66	99-110	DGSDYDLTGYIIDNMYD (SEQ ID NO: 2154)
1031O03	861	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-116	GYSASRAFDI (SEQ ID NO: 2136)
1031C07	862	147-258	170-183	199-205	238-247	1-131	26-35	50-66	99-120	SSPRWYDALTGDSSSYHSAMDV (SEQ ID NO: 2169)
1031F09	863	143-255	167-179	195-201	234-244	1-127	26-35	50-66	99-116	DEGRDLLTGYWPNFDS (SEQ ID NO: 2168)
1031G08	864	147-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120	SSPKWYDALTGHSYHSAMDV (SEQ ID NO: 2158)
1031G10	865	147-258	170-182	198-204	237-248	1-131	26-35	50-66	99-120	SSPKWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1031G11	866	143-255	167-179	195-201	234-244	1-127	26-35	50-66	99-116	DEGRDLLTGYWPNFDS (SEQ ID NO: 2165)
1037E07	867	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	DGDIILLVPAALMDV (SEQ ID NO: 2168)
1037E12	868	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	DGDIILLVPAALMDV (SEQ ID NO: 2160)
1050A07	869	145-257	168-181	197-203	236-246	1-129	26-40	55-71	104-118	QNDPLTGYKLGFDY (SEQ ID NO: 2160)
1061D02	870	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	DRYDILTGYYYYGMDV (SEQ ID NO: 2164)
1061E07	871	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1061H01	872	146-256	168-181	197-203	236-245	1-130	26-35	50-66	101-119	FNPYDILTGYVIGYGFQI (SEQ ID NO: 2155)
1001A03	873	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	ERHYDILTGYQYGYGMDV (SEQ ID NO: 2153)
1001A07	874	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001A08	875	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001A10	876	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001A12	877	141-248	162-172	188-194	227-237	1-121	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001B02	878	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	DRETKVGYGMDV (SEQ ID NO: 2945)
1001B07	879	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001C06	880	143-253	165-178	194-200	233-242	1-127	26-33	48-64	97-116	EGGNYDILTGYVIGNGAFDI (SEQ ID NO: 2158)
1001C08	881	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	EGSYDILTGYVIGVGRMDV (SEQ ID NO: 2171)
1001C12	882	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001D08	883	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-114	DSYDILTGYRGGYEDY (SEQ ID NO: 2745)
1001D12	884	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001E05	885	143-253	165-178	194-200	233-242	1-127	26-33	48-64	97-116	EGGNYDILTGYVIGNGAFDI (SEQ ID NO: 2158)
1001F07	886	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001G09	887	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1001H05	888	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	ERHYDILTGYQYGYGMDV (SEQ ID NO: 2784)
1001H08	889	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1003A01	890	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSVGGATTGALDM (SEQ ID NO: 2852)
1003A06	891	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSVGGATTGALDM (SEQ ID NO: 2852)
1003A07	892	142-249	163-172	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYVIGMDV (SEQ ID NO: 2135)
1003A10	893	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYVGGYEDY (SEQ ID NO: 2179)

1003B03	894	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSVGGATTGALDM (SEQ ID NO: 2852)
1003B04	895	138-248	162-172	188-194	227-237	1-122	25-34	49-65	98-111	RYGDPFYNNMNV (SEQ ID NO: 2755)
1003B09	896	142-249	163-175	189-195	228-238	1-126	26-35	50-66	98-113	DGYDILTGYYGMDV (SEQ ID NO: 2135)
1003C01	897	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGSSVGGATTGALDM (SEQ ID NO: 2174)
1003C02	898	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	GDYDILTGYPACFCQ (SEQ ID NO: 2854)
1003C03	899	141-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	GDYDILTGYPACFCQ (SEQ ID NO: 2854)
1003C12	900	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGDFY (SEQ ID NO: 2854)
1003D04	901	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-114	RYGDPFYNNMNV (SEQ ID NO: 2179)
1003E05	902	141-253	164-176	192-198	231-242	1-125	26-35	50-66	99-114	DGYDILTGYPACFCQ (SEQ ID NO: 2854)
1003F01	903	139-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGSSVGGATTGALDM (SEQ ID NO: 2852)
1003F02	904	143-254	168-179	195-201	234-243	1-127	26-35	50-66	99-112	RYGDPFYNNMNV (SEQ ID NO: 2755)
1003G01	905	143-254	168-179	195-201	234-243	1-127	26-35	50-66	99-112	GTGYDILTGYYGSAFDQ (SEQ ID NO: 2800)
1003G05	906	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GSYDILTGYYGSPLDY (SEQ ID NO: 2766)
1003G06	907	145-256	168-181	197-203	236-245	1-129	26-35	50-66	99-118	DRGNYDILTGYYHHGVDV (SEQ ID NO: 2914)
1003G11	908	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DAQSYDILTGYSYAFDI (SEQ ID NO: 2183)
1003H02	909	140-253	164-176	192-198	231-242	1-124	26-35	50-66	99-113	DNYDILTGYSRRDP (SEQ ID NO: 2942)
1003H05	910	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSVGGATTGALDM (SEQ ID NO: 2852)
1003H08	911	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYYGMDV (SEQ ID NO: 2135)
1005A01	912	141-249	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SHYDILTGLNWYFDL (SEQ ID NO: 2166)
1005A02	913	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	EGRDILTGYYGGLDV (SEQ ID NO: 2893)
1005B01	914	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SHYDILTGLNWYFDL (SEQ ID NO: 2166)
1005B09	915	137-247	159-172	188-194	227-236	1-121	26-35	50-65	98-110	TYDILTGRFFDI (SEQ ID NO: 2866)
1005C01	916	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DLRYDILTGYYHDAFDI (SEQ ID NO: 2890)
1005D02	917	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	GAYDILTGYYGMDV (SEQ ID NO: 2860)
1005D03	918	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	GTYYDILTGYYHGMVDY (SEQ ID NO: 2774)
1005E01	919	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	SHYDILTGLNWYFDL (SEQ ID NO: 2166)
1005F08	920	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	DQHDILTGYYGMDV (SEQ ID NO: 2921)
1005F09	921	140-248	164-174	190-196	229-238	1-124	26-35	50-66	99-113	VSPSYDILTGYYHAFDV (SEQ ID NO: 2849)
1005F02	922	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117	TYDILTGRFFDI (SEQ ID NO: 2866)
1005F04	923	137-247	159-172	188-194	227-236	1-121	26-35	50-65	98-110	PSYDILTGYYHDAFDI (SEQ ID NO: 2850)
1005F08	924	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	DLRYDILTGYYHDAFDI (SEQ ID NO: 2890)
1005G01	925	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	GAYDILTGYYGMDV (SEQ ID NO: 2860)
1005G08	926	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	QGYDILTGYYWDFP (SEQ ID NO: 2857)
1005H02	927	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	SRDILTFPHYGMDV (SEQ ID NO: 2133)
1006B01	928	139-246	160-170	186-192	225-235	1-127	26-35	50-66	99-112	GGYSSGWLRCGPYNWDFP (SEQ ID NO: 2967)
1006C09	929	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116	

1006D09	930	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	GDYDILTGYPIRLDY (SEQ ID NO: 2792)
1006E01	931	143-253	165-178	194-200	233-242	1-127	26-35	50-68	101-116	NLFDDVWTLPPYYMDY (SEQ ID NO: 2965)
1006E07	932	143-250	166-176	192-198	231-239	1-127	26-35	50-68	99-116	ADYDILGTSPLYTGMVD (SEQ ID NO: 2762)
1006F02	933	143-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113	MYDILTGHNFYD (SEQ ID NO: 2879)
1006F07	934	142-253	164-176	192-198	231-242	1-127	26-35	50-66	99-115	VSRDILGTNYYYGYMDY (SEQ ID NO: 2817)
1006F07	935	143-253	165-177	193-199	232-242	1-126	26-35	50-66	99-116	GGYSSGWLKGGPPYNDP (SEQ ID NO: 2967)
1006G01	936	146-253	169-179	195-201	234-242	1-130	26-35	50-68	101-119	AGGYDILGTGRDYYGYMDY (SEQ ID NO: 2877)
1006G04	937	132-239	153-163	179-185	218-228	1-116	26-35	50-68	99-105	RRYALDY (SEQ ID NO: 2920)
1006H01	938	146-253	167-177	193-199	232-242	1-126	26-35	50-65	98-119	DRGSDILGTYPHYGYMDV (SEQ ID NO: 2761)
1006H02	939	143-253	165-177	192-198	231-240	1-127	26-35	50-66	99-116	GGYSSGWLKGGPPYNDP (SEQ ID NO: 2967)
1007A01	940	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)
1007A08	941	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-114	SHYDILTGLNYWYFDY (SEQ ID NO: 2153)
1007A11	942	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ENYDILTGYGAFDI (SEQ ID NO: 2772)
1007A12	943	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117	GIYDILTGYHWDGAFDI (SEQ ID NO: 2892)
1007B04	944	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)
1007C04	945	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)
1007C08	946	142-249	163-173	189-195	228-238	1-126	26-35	50-65	98-115	IRLYCSLTGYYPYGMDD (SEQ ID NO: 2810)
1007C12	947	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	QYDYLTYGYNWFDY (SEQ ID NO: 2882)
1007D07	948	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	QYDYLTYGYNWFDY (SEQ ID NO: 2882)
1007D08	949	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117	GIYDILTGYHWDGAFDI (SEQ ID NO: 2872)
1007E03	950	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)
1007E10	951	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SHYDILTGLNYWYFDI (SEQ ID NO: 2811)
1007E11	952	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-114	DFYDILTYGYPGMDY (SEQ ID NO: 2741)
1007F06	953	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-117	DLPPYDILTYGSLTSGMDY (SEQ ID NO: 2923)
1007F08	954	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	GRYDILTYGYYHHGMDV (SEQ ID NO: 2853)
1007G09	955	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SHYDILTGLNYWYFDI (SEQ ID NO: 2811)
1007G10	956	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DSGGBILTYGMPYFDY (SEQ ID NO: 2166)
1007H07	958	147-257	169-182	198-204	237-246	1-131	26-35	50-65	98-115	VLGYDILTYGYPGMDY (SEQ ID NO: 2805)
1007H11	959	141-248	162-172	188-194	227-237	1-125	26-35	50-68	101-120	SOAHYDILTYGSLTSGMDY (SEQ ID NO: 2875)
1008A02	960	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ESYDILTYGRHYGMDI (SEQ ID NO: 2891)
1008A05	961	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)
1008A06	962	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)
1008A07	963	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DREYDILTYGSLTSGMDY (SEQ ID NO: 2153)
1008A12	964	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ENYDILTYGYPGMDY (SEQ ID NO: 2960)
1008B02	965	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO: 2153)

1008B04	966	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DGSDILTGYYDNYMDV (SEQ ID NO: 2154)
1008B05	967	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	DHYDILTGYYGMDV (SEQ ID NO: 2760)
1008B06	968	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008B07	969	140-247	163-173	185-195	228-236	1-124	26-33	48-64	97-113	GRYDILTGYYKGPLDY (SEQ ID NO: 2902)
1008B10	970	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	AYDNLITGLPYGMGV (SEQ ID NO: 2947)
1008B11	971	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EYDNLITGYFLDYHGMVDV (SEQ ID NO: 2753)
1008C06	972	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008C08	973	149-259	171-183	189-205	238-248	1-133	26-35	50-66	99-112	PRGGPYDILTGYYLSLSDAFDI (SEQ ID NO: 2729)
1008C09	974	142-249	163-173	185-195	228-238	1-126	26-35	50-66	99-112	EGYDILTGYSFGDFI (SEQ ID NO: 2153)
1008D01	975	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008D02	976	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008D03	977	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008D04	978	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-117	EVNRYDILTRSYLAGPLDN (SEQ ID NO: 2751)
1008D05	979	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008D06	980	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008D07	981	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DRGYDILTGYYRGHGMVDV (SEQ ID NO: 2837)
1008D08	982	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DLPYDILTGYSLTSGMDV (SEQ ID NO: 2923)
1008D12	983	144-254	166-179	195-201	234-240	1-128	26-35	50-66	99-117	EGFYDILTGYYGFGYEDY (SEQ ID NO: 2974)
1008E01	984	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	EGYDILTGYSKFLDY (SEQ ID NO: 2906)
1008E02	985	137-247	159-172	188-194	227-236	1-121	20-31	46-63	96-110	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008E03	986	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008E04	987	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SHYDILTGLNYYWYFDL (SEQ ID NO: 2166)
1008E08	988	141-252	163-175	191-197	230-241	1-125	26-35	50-66	99-114	ERADYDILTGYYFYDMDV (SEQ ID NO: 2833)
1008E09	989	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	FRYDILTGYSFGMDV (SEQ ID NO: 2734)
1008E12	990	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008F03	991	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008F06	992	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	GRYDILTGYYHHGMDV (SEQ ID NO: 2811)
1008F07	993	143-250	164-174	190-196	229-239	1-127	26-35	50-65	98-116	GHYDILTGYYDYYGMDV (SEQ ID NO: 2844)
1008F08	994	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	HDILTGFEDY (SEQ ID NO: 2904)
1008F10	995	133-243	155-168	184-190	223-232	1-117	26-35	50-65	98-106	SGYDILTGYYGMDV (SEQ ID NO: 2934)
1008F11	996	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	APYDILTGYSDDYGMVDV (SEQ ID NO: 2968)
1008G02	997	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117	ATYDPLTGYSFGDFI (SEQ ID NO: 2153)
1008G03	998	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	GDYDPLTGYSFGVDV (SEQ ID NO: 2941)
1008G04	999	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	EGSYDILTGYYGVGRMDV (SEQ ID NO: 2171)
1008G05	1000	143-252	166-178	194-200	233-242	1-127	26-35	50-65	98-116	DGYDILTGYYGYYGMDV (SEQ ID NO: 2899)
	1001	144-254	165-179	195-201	234-243	1-128	26-35	50-66	99-117	



1008G11	1002	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	AYTDILTGLDY (SEQ ID NO: 2966)
1008G12	1003	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DQQYDILGYHYHGMVD (SEQ ID NO: 2964)
1008H02	1004	141-248	164-176	190-196	229-237	1-125	26-35	50-66	99-114	QYDYLMLDHNHYMDV (SEQ ID NO: 2964)
1008H03	1005	141-251	163-174	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2918)
1008H06	1006	143-253	165-178	194-200	233-242	1-127	26-35	50-66	98-116	EGSYDILGYVGVGRMDV (SEQ ID NO: 2153)
1008H09	1007	143-253	165-178	194-200	233-242	1-127	26-35	50-66	98-116	DQYDILGYHYHGMVD (SEQ ID NO: 2171)
1008H11	1008	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	TKYDILTYGYYHYMDV (SEQ ID NO: 2856)
1012B03	1009	140-249	163-175	191-197	230-238	1-124	26-34	50-66	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012B06	1010	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012B10	1011	142-255	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012C03	1012	142-255	165-178	194-200	233-244	1-126	26-35	50-66	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012C06	1013	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	TDREKADVTSRWGMVD (SEQ ID NO: 2814)
1012C09	1014	140-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012D12	1015	145-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118	DRGNYDILTYHYHGHGVDV (SEQ ID NO: 2914)
1012E07	1016	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	RYGDPFYHYHGMVDV (SEQ ID NO: 2174)
1012E08	1017	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	ELGLSVGATTGALDM (SEQ ID NO: 2755)
1012E09	1018	140-247	163-173	189-195	228-236	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012F05	1019	140-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012F12	1020	140-251	164-176	192-198	231-240	1-124	26-34	49-65	99-112	RYGDPFYHYHGMVDV (SEQ ID NO: 2755)
1012G03	1021	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1012G05	1022	139-250	163-173	189-195	228-239	1-123	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
1012G10	1023	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
1012H09	1024	140-249	163-173	189-195	228-238	1-124	26-34	49-65	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2165)
1013A10	1025	147-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
1013A12	1026	147-256	171-181	197-203	236-245	1-131	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013B04	1027	147-256	172-182	198-204	237-245	1-131	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013B09	1028	147-257	171-181	197-203	236-246	1-131	26-35	50-66	99-118	GLRHLVLTGTRGHYHGMVDV (SEQ ID NO: 2789)
1013C02	1029	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	GREDTCKVFPWDRYHYHGMVDV (SEQ ID NO: 2809)
1013C04	1030	137-249	161-173	189-195	228-238	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013D02	1031	137-248	160-173	189-195	228-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013D03	1032	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2165)
1013D10	1033	145-257	168-181	197-203	236-246	1-129	26-35	50-66	99-118	GLRHLVLTGTRGHYHGMVDV (SEQ ID NO: 2789)
1013E02	1034	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	GREDTCKVFPWDRYHYHGMVDV (SEQ ID NO: 2809)
1013E05	1035	137-249	162-173	189-195	228-238	1-121	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
1013E09	1036	147-260	170-183	199-205	238-249	1-131	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2165)
1013F03	1037	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)

1013F04	1038	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SPPKWYDALTGHSYHSAMDY (SEQ ID NO: 2159)
1013F07	1039	145-260	170-185	201-207	240-249	1-129	26-35	50-66	99-118	AATTSOKHNKYAYTYGMVDY (SEQ ID NO: 2131)
1013F09	1040	137-249	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013F10	1041	147-259	170-182	198-205	238-248	1-131	26-35	50-66	99-120	SPPKWYDALTGHSYHSAMDY (SEQ ID NO: 2159)
1013H04	1042	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SPPKWYDALTGHSYHSAMDY (SEQ ID NO: 2159)
1013H07	1043	147-259	170-183	198-205	238-248	1-131	26-35	50-66	99-120	GREDTGYKWPDRYHYHYMDY (SEQ ID NO: 2809)
1014A12	1044	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGNVDYLTGYVINGAFDI (SEQ ID NO: 2158)
1014C06	1045	141-254	164-177	193-200	233-243	1-125	26-35	50-66	99-114	GYDILTYGPAECFQI (SEQ ID NO: 2854)
1014C10	1046	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1014C12	1047	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1014E06	1048	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1014F02	1049	141-251	166-176	192-198	231-240	1-125	26-37	52-67	100-114	AGYDILTYGPFYFDS (SEQ ID NO: 2175)
1016A08	1050	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	EVKNYDLTSLYAGPLDN (SEQ ID NO: 2751)
1016A09	1051	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016C02	1052	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016C03	1053	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016C05	1054	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016C09	1055	141-251	163-176	192-198	231-240	1-132	26-35	50-66	99-121	VQMDSEYDILLTGINVGPFYFDY (SEQ ID NO: 2132)
1016C11	1056	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016D10	1057	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-121	VQMDSEYDILLTGINVGPFYFDY (SEQ ID NO: 2132)
1016D11	1058	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016E03	1059	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016E04	1060	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016F03	1061	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016F11	1062	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016G01	1063	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016G06	1064	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016G12	1065	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1016H10	1066	141-251	163-176	192-198	231-240	1-132	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1017A06	1067	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-121	VQMDSEYDILLTGINVGPFYFDY (SEQ ID NO: 2132)
1017A07	1068	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1017A11	1069	140-253	162-175	191-197	233-242	1-124	25-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1017E12	1070	141-251	163-176	192-198	231-240	1-124	25-34	49-65	98-113	ATYDPLTGYSDGFDI (SEQ ID NO: 2157)
1017G03	1071	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1017G07	1072	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1017H01	1073	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)

to BLYS on U937 membranes or to histidine-tagged BLYS. In this assay, antibodies are added to 96 well plates coated with U937 membranes or histidine-tagged BLYS and those antibodies or antibody fragments or variants that bind to the U937 membranes or histidine-tagged BLYS are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants thereof) that do not bind to biotinylated BLYS (soluble BLYS) but bind to membrane-bound BLYS, such as, for example, that on membranes from U937 cells (see Example 2, *infra*). In these assays, soluble BLYS (e.g., biotinylated BLYS) and membrane-bound BLYS (e.g., on U937 membranes) are incubated in separate samples with the same antibodies (or antibody fragments or variants) and those antibodies (or antibody fragments or variants) that do not bind to the soluble BLYS (biotinylated BLYS), but bind the membrane-bound BLYS (e.g., on U937 membranes) are captured and identified. In other assays, antibodies are screened using ELISAs to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged BLYS or membranes from U937 cells do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (See Example 4, *infra*). ELISAs can also be used to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged BLYS or membranes from U937 cells bind to BLYS in the presence of TNF-alpha (see Example 4, *infra*). Antibodies or fragments or variants thereof that immunospecifically bind to the membrane-bound form of BLYS may also be tested for their affinity for histidine-tagged BLYS using high-throughput BIAcore analysis (see Example 14, *infra*).

**[0333]** Additionally, antibodies of the invention may be screened against cells engineered to express an “uncleavable” form of BLYS in order to determine their specificity for the membrane-bound form of BLYS. Mutations in BLYS which may achieve this result include, but are not limited to, the mutation or deletion of amino acid residues Lys-132 and/or Arg-133 of the BLYS sequence shown in SEQ ID NO:3228. A typical mutagenesis might include mutation of one or both of residues Lys-132 or Arg-133 to alanine residues. Cells expressing such an “uncleavable” form of BLYS provide a profound reagent to use in assaying the ability of antibodies to bind the membrane-bound form of BLYS.

Selection and Screening for Antibodies that Immunospecifically Bind to Soluble and Membrane-bound BLyS

**[0334]** Antibodies of the invention (including scFvs and other molecules comprising, or alternately consisting of, antibody fragments or variants) may be screened in a variety of assays to identify those antibodies or antibody fragments or variants that immunospecifically bind to the soluble form and membrane-bound form of BLyS. In one particular assay, antibodies that bind to immobilized BLyS are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that inhibit the binding of soluble BLyS (e.g. soluble bio-BLyS) to IM-9 cells as described *supra*. In other assays, antibodies are screened using ELISAs for those antibodies that bind to membranes from U937 cells. Additionally, further ELISA assays may be performed using techniques known in the art to determine which antibodies do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS, or those antibodies that bind to BLyS in the presence of TNF-alpha (see Example 4 *infra*). Antibodies may be assayed in neutralization assays using techniques described herein or otherwise known in the art. Antibodies that immunospecifically bind to the soluble and membrane-bound forms of BLyS may also be tested for their affinity for BLyS using high-throughput BIAcore analysis.

Antibody Conjugates

**[0335]** The present invention encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous polypeptides to particular cell types (e.g., cells of monocytic lineage and B-cells), either *in vitro* or *in vivo*, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that are specific for particular cell surface antigens (e.g., membrane-bound BLyS on cells of monocytic lineage) or which bind antigens that bind particular cell surface receptors (e.g.,

TACI and/or BCMA located on B cells). Antibodies fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See *e.g.*, Harbor *et al.*, supra, and PCT publication WO 93/2 1232; EP 439,095; Naramura *et al.*, Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies *et al.*, PNAS 89:1428-1432 (1992); Fell *et al.*, J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

**[0336]** In one embodiment, a fusion protein comprises a polypeptide having an amino acid sequence of any one of the VH domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 (i.e., SEQ ID NOS:2129 - 3227), and a heterologous polypeptide.

**[0337]** In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, and a heterologous polypeptide. In yet another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR3s referred to in Table 1, and a heterologous polypeptide.

**[0338]** In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, and one or more VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein of the present invention comprises a polypeptide having the amino acid sequence of any one of the VH CDRs referred to in Table 1, and any one of the VL CDRs referred to in Table 1, and a heterologous polypeptide.

**[0339]** The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)<sub>2</sub> fragment, or a portion thereof. Methods for fusing or conjugating polypeptides to antibody portions are known in the art. See, *e.g.*, U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 9 1/06570; Ashkenazi *et al.*, Proc. Natl. Acad. Sci. USA 88: 10535-10539 (1991); Zheng *et al.*, J. Immunol. 154:5590-5600 (1995); and Vil *et al.*, Proc. Natl. Acad. Sci. USA 89:11337- 11341 (1992) (said references incorporated by reference in their entireties).

**[0340]** Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered activity (*e.g.*, antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten *et al.*, Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, *et al.*, J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, polynucleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody which portions immunospecifically bind to BLYS may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

**[0341]** Moreover, the antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexahistidine polypeptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton

Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, Cell 37:767 (1984)) and the "flag" tag (DYKDDDDK, (SEQ ID No: 3238) Stratagene, La Jolla, CA).

**[0342]** The present invention further encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor or prognose the development or progression of a tumor as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include, but are not limited to, streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples of suitable radioactive material include, but are not limited to, iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon

(<sup>133</sup>Xe), fluorine (<sup>18</sup>F), <sup>153</sup>Sm, <sup>177</sup>Lu, <sup>159</sup>Gd, <sup>149</sup>Pm, <sup>140</sup>La, <sup>175</sup>Yb, <sup>166</sup>Ho, <sup>90</sup>Y, <sup>47</sup>Sc, <sup>186</sup>Re, <sup>188</sup>Re, <sup>142</sup>Pr, <sup>105</sup>Rh, <sup>97</sup>Ru, <sup>68</sup>Ge, <sup>57</sup>Co, <sup>65</sup>Zn, <sup>85</sup>Sr, <sup>32</sup>P, <sup>153</sup>Gd, <sup>169</sup>Yb, <sup>51</sup>Cr, <sup>54</sup>Mn, <sup>75</sup>Se, <sup>113</sup>Sn, and <sup>117</sup>Tin.

**[0343]** Further, an antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof), may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi. In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, <sup>111</sup>In, <sup>177</sup>Lu, <sup>90</sup>Y, <sup>166</sup>Ho, and <sup>153</sup>Sm, to polypeptides. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is <sup>111</sup>In. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is <sup>90</sup>Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90, 1998; Peterson et al., Bioconjug. Chem. 10(4):553-7, 1999; and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

**[0344]** A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells and includes such molecules as small molecule toxins and enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof. Examples include, but are not limited to, paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide (VP-16), teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNase, and puromycin and fragments, variants or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan,



dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin, anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine), improsulfan, pipsulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate trimethylolmelamine, chlornaphazine, cholophosphamide, estramustine, ifosfamide, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine, aclacinomysins, azaserine, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, chromomycins, detorubicin, 6-diazo-5-oxo-L-norleucine, epirubicin, esorubicin, idarubicin, marcellomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, quelamycin, rodorubicin, streptonigrin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, thiamiprine, ancitabine, azacitidine, 6-azauridine, carmofur, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU, calusterone, dromostanolone propionate, epitioctanol, mepitiostane, testolactone, aminogluthethimide, mitotane, trilostane, frolic acid, aceglutone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, dernecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllin acid, 2-ethylhydrazide, procarbazine, PSKO, razoxane, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2, 2',2"-trichlorotriethylamine, urethan, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), taxoids, *e.g.* paclitaxel (TAXOL", Bristol-Myers Squibb Oncology, Princeton, NJ) doxetaxel (TAXOTERE", Rhône-Poulenc Rorer, Antony, France), gemcitabine, ifosfamide, vinorelbine, navelbine, novantrone, teniposide, aminopterin, xeloda, ibandronate, CPT-11, topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, esperamicins, capecitabine, and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene,

keoxifene, LY 117018, onapristone, toremifene (Fareston), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, and pharmaceutically acceptable salts, acids or derivatives of any of the above.

**[0345]** Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (e.g., Bolton-Hunter and Chloramine-T reaction).

**[0346]** The antibodies of the invention which are conjugates can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

**[0347]** Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

**[0348]** Techniques for conjugating a therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In

Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0349] Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0350] An antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

#### Use of Antibodies for Epitope Mapping

[0351] The present invention provides antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that can be used to identify epitopes of BLyS. In particular, the antibodies of the present invention can be used to identify epitopes of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes) using techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211.)

#### Diagnostic Uses of Antibodies

**[0352]** Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of BLyS or BLyS receptor. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLyS compared to the standard level of BLyS is indicative of aberrant expression.

**[0353]** By “biological sample” is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, or other source which may contain BLyS protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, spinal fluid, saliva, and mucous. Tissues samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

**[0354]** The invention also provides for the detection of aberrant expression of BLyS receptor comprising (a) assaying the expression of BLyS receptor in a biological sample from an individual using one or more antibodies or fragments or variants thereof that immunospecifically binds only to soluble BLyS, but does not inhibit BLyS /BLyS receptor binding. Such an antibody, by way of an example that is not to be construed as limiting, would be one that is able to capture a biotinylated BLyS from solution (see Example 8), but that would not prevent BLyS from binding to IM-9 cells (see Example 3). and (b) comparing the level of BLyS receptor with a standard level of BLyS receptor, *e.g.*, in normal tissue or cell samples, whereby an increase or decrease in the assayed level of BLyS receptor compared to the standard level of BLyS receptor is indicative of aberrant expression.

**[0355]** Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLYS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of BLYS comprising: (a) assaying the expression of BLYS in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLYS; and (b) comparing the level of BLYS with a standard level of BLYS, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLYS compared to the standard level of BLYS is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of BLYS is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of BLYS is indicative of an immunodeficiency.

**[0356]** Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLYS but, do not inhibit BLYS/BLYS receptor binding can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of BLYS receptor comprising: (a) assaying the expression of BLYS receptor in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLYS; and (b) comparing the level of BLYS receptor with a standard level of BLYS receptor, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLYS receptor compared to the standard level of BLYS receptor is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of BLYS receptor is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of BLYS receptor is indicative of an immunodeficiency.

**[0357]** Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmune cytopenia,

hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henoch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus), juvenile onset diabetes, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease , (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia (Addison's disease), idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders and other disorders such as inflammatory skin diseases including psoriasis and sclerosis, responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), respiratory distress syndrome (including adult respiratory distress syndrome, ARDS), meningitis, encephalitis, colitis, allergic conditions such as eczema and other conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, leukocyte adhesion deficiency, Reynaud's syndrome, and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, granulomatosis and diseases involving leukocyte diapedesis, central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, Lambert-Eaton myasthenic syndrome, Behcet disease, giant cell arteritis, immune complex nephritis, IgA

nephropathy, IgM polyneuropathies or autoimmune thrombocytopenia etc.

**[0358]** In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

**[0359]** Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

**[0360]** Elevated levels of soluble BLyS have been observed in the serum of patients with Systemic Lupus Erythematosus (SLE). In comparing the sera of 150 SLE patients with that of 38 control individuals, it was found that most of the SLE patients had more than 5ng/ml of serum BLyS, more than 30% of SLE patients had levels greater than 10ng/ml, and approximately 10% of SLE patients had serum BLyS levels greater than

20ng/ml. In contrast, the majority of normal controls had BLyS levels less than 5ng/ml, and less than 10% had levels higher than 10ng/ml. The elevated levels of BLyS protein in sera is present in the soluble form and has biologic activity as assayed by the ability to stimulate anti-IgM treated B cells in vitro. SLE patients with more than 15ng/ml serum BLyS were also found to have elevated levels of anti-dsDNA antibodies compared to both normal controls and SLE patients with less than 5ng/ml of serum BLyS.(unpublished data).

**[0361]** In addition the serum of two subgroups of patients which were positive for anti-nuclear antibodies (ANA+) but did not meet the formal requirements of the American College of Rheumatology (ACR) for classification of SLE were analyzed for BLyS levels. The first subgroup of sera was ANA+ sera that came from patients who did not present with the clinical impression of SLE. This group had only slightly elevated levels of BLyS (~9ng/ml BLyS). The second subgroup however, which was ANA+ sera from patients who presented with the clinical impression of SLE, had significantly increased BLyS levels (~15ng/ml). These results suggest that an elevated level of BLyS precedes the formal fulfillment of the ACR criteria. The ACR criteria are described in Tan, E.M., et al, *Arthritis and Rheumatism* 25:1271 – 1277 (1982).

**[0362]** Thus in specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Systemic Lupus Erythematosus or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, e.g., in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of SLE.

**[0363]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor IgA nephropathy or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of



BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of IgA nephropathy.

**[0364]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Sjögren's Syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Sjögren's Syndrome.

**[0365]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor HIV infection or conditions associated therewith (*e.g.* AIDS). The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of HIV infection.

**[0366]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Myasthenia Gravis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Myasthenia Gravis.

**[0367]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose,

prognose, or monitor idiopathic thrombocytopenic purpura (ITP) or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of idiopathic thrombocytopenic purpura (ITP).

**[0368]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor hemolytic anemia or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of hemolytic anemia.

**[0369]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor thyroiditis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of thyroiditis.

**[0370]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Goodpasture's syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby

an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Goodpasture's syndrome.

**[0371]** In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor multiple sclerosis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of multiple sclerosis.

**[0372]** In additional embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Rheumatoid Arthritis. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample (*e.g.*, serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Rheumatoid arthritis.

**[0373]** In additional embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor an immune-based rheumatologic disease, (*e.g.*, SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), Polymyositis/dermatomyositis, Microscopic polyangiitis, Hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder). The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample (*e.g.*, serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an

increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of monitor an immune-based rheumatologic disease.

[0374] It has been observed, that serum BLyS levels inversely correlate with nephrotic range proteinuria ( $>3\text{gm}$  proteinuria in a 24 hour urine collection) using a sample of 71 SLE patients ( $p=0.019$ ). Proteinuria was determined in 71 SLE patients within one month of phlebotomy for serum BLyS determination. Serum BLyS was classified as low, normal, or high based on the 5<sup>th</sup> through 95<sup>th</sup> percentiles for normal controls. Nephrotic-range proteinuria was inversely correlated with serum Neutrokin- $\alpha$  levels. Thus, in specific embodiments, serum levels of BLyS (determined using one or more antibodies of the present invention) in individuals diagnosed with an immune based rheumatologic disease (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder) may be used to determine, diagnose, prognose, or monitor the severity of certain aspects or symptoms of the disease, such as nephrotic-range proteinuria.

[0375] In another specific embodiment, antibodies of the invention are used to diagnose, prognose, treat, or prevent conditions associated with CVID, including, but not limited to, conditions associated with acute and recurring infections (e.g., pneumonia, bronchitis, sinusitis, otitis media, sepsis, meningitis, septic arthritis, and osteomyelitis), chronic lung disease, autoimmunity, granulomatous disease, lymphoma, cancers (e.g., cancers of the breast, stomach, colon, mouth, prostate, lung, vagina, ovary, skin, and melanin forming cells (i.e. melanoma), inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and ulcerative proctitis), malabsorption, Hodgkin's disease, and Waldenstrom's macroglobulinemia.

[0376] The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLyS; and (b) comparing the level of BLyS with a standard BLyS level, e.g., in a biological sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed BLyS level compared to the standard level of BLyS is indicative

of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of BLyS in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

**[0377]** In specific embodiments, the presence of a relatively high amount of membrane-bound BLyS in a biological sample is indicative of monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia and/or the severity thereof.

**[0378]** In other specific embodiments, the presence of a relatively high amount of BLyS receptor in a biological sample (as determined using antibodies of the invention that bind to soluble BLyS, but do not inhibit BLyS/BLyS receptor binding) is indicative of B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease), and/or the severity thereof.

**[0379]** In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing Systemic Lupus Erythematosus, comprising: (a) assaying for the level of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLyS; and (b) comparing the level of BLyS with a standard BLyS level, e.g., in a biological sample from a patient without Systemic Lupus Erythematosus, whereby an increase in the assayed BLyS level compared to the standard level of BLyS is indicative of Systemic Lupus Erythematosus.

**[0380]** In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing a Rheumatoid Arthritis, comprising: (a) assaying for the level of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLyS; and (b) comparing the level of BLyS with a standard BLyS level, e.g., in a biological sample from a patient without Rheumatoid Arthritis, whereby an increase or decrease in the assayed BLyS level compared to the standard level of BLyS is indicative of Rheumatoid Arthritis.

**[0381]** The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of BLyS receptor in cells or a tissue sample of an individual using one or more antibodies of the invention that

immunospecifically binds only to soluble BLyS, but does not neutralize BLyS /BLyS receptor binding; and (b) comparing the level of BLyS receptor with a standard BLyS receptor level, e.g., in a tissue sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed BLyS receptor level compared to the standard level of BLyS receptor is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of BLyS receptor in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

**[0382]** Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can be used to assay protein levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (e.g., see Jalkanen, *et al.*, J. Cell. Biol. 101:976-985 (1985); Jalkanen, *et al.*, J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, alkaline phosphatase, and horseradish peroxidase; radioisotopes, such as iodine ( $^{121}\text{I}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{111}\text{In}$ ,  $^{112}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{115\text{m}}\text{In}$ ), technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ , and  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[0383]** One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of BLyS or BLyS receptor in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or

1026E06	1146	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	GYDDLTYGYNALDY (SEQ ID NO: 2821)
1026E09	1147	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026F01	1148	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026F09	1149	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026F12	1150	140-256	163-176	192-202	237-245	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026G08	1151	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026G10	1152	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026G11	1153	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GTGYDLTYGYYGSAFQI (SEQ ID NO: 2800)
1026H02	1154	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYNNV (SEQ ID NO: 2755)
1026H06	1155	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2174)
1026H10	1156	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	GGEYDLTYGYYGLGVYDY (SEQ ID NO: 2170)
1027A09	1157	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027B02	1158	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYNNV (SEQ ID NO: 2755)
1027B05	1159	140-250	163-176	192-198	230-239	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027C08	1160	138-249	161-174	190-196	229-238	1-122	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027D02	1161	141-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	DPEGAAPGYYYAMDV (SEQ ID NO: 2826)
1027E03	1162	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027F05	1163	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027F04	1164	144-252	167-176	192-198	231-241	1-128	26-35	50-66	99-117	GPWYDLPPSPGRHYGLDV (SEQ ID NO: 2174)
1027F05	1165	140-254	163-176	192-198	231-243	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2174)
1027F11	1166	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027G06	1167	140-253	164-176	192-198	233-242	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027G07	1168	140-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027H03	1169	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	ATYDPLTYGSRFDP (SEQ ID NO: 2942)
1028A04	1170	143-250	164-174	190-196	229-239	1-123	26-35	50-66	99-114	ELGSSIVGATTGALDM (SEQ ID NO: 2174)
1028A07	1171	141-251	163-176	192-198	231-240	1-127	26-35	50-66	99-116	GDYDLTYGPAECFQI (SEQ ID NO: 2854)
1028B06	1172	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DMYDILTYGYYTGLAFDM (SEQ ID NO: 2880)
1028B10	1173	148-258	170-183	199-205	238-247	1-132	26-35	50-66	99-114	VLNYDILTYGYYGMDV (SEQ ID NO: 2832)
1028C01	1174	142-250	165-175	191-197	230-239	1-126	26-37	52-69	101-121	ATYDPLTYGSRFDP (SEQ ID NO: 2153)
1028C04	1175	143-253	165-178	194-200	233-242	1-127	26-35	50-66	102-115	GGHTCHPTCHMG (SEQ ID NO: 2796)
1028C08	1176	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DMYDILTYGYYTGLAFDM (SEQ ID NO: 2880)
1028D04	1177	140-247	163-173	189-195	228-236	1-124	26-35	50-65	98-113	ATYDPLTYGSRFDP (SEQ ID NO: 2153)
1028D05	1178	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	EHYDILTYGSLGMDV (SEQ ID NO: 2907)
1028D12	1179	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DGYDILTYGYYGMDV (SEQ ID NO: 2938)
1028E06	1180	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	EGSYDILTYGYYGGRMDV (SEQ ID NO: 2171)
1028E07	1181	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTYGSRFDP (SEQ ID NO: 2153)

1028E08	1182	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1028F06	1183	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	DKRGYYDILTYGRFGSDI (SEQ ID NO: 2901)
1028F08	1184	143-251	163-176	185-191	224-233	1-118	26-35	50-66	99-107	DIGJGGDS (SEQ ID NO: 2954)
1028F08	1185	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	VSYNSGYFSYDMV (SEQ ID NO: 2732)
1028G10	1186	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLITRSLAGPLDN (SEQ ID NO: 2751)
1028G10	1187	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1028H02	1188	142-249	165-175	191-197	230-238	1-126	26-37	52-69	102-115	SEGPITLACNLGG (SEQ ID NO: 2797)
1028H03	1189	148-256	169-179	195-201	234-245	1-132	26-35	50-66	99-118	DASEYDILTYGLTYATGRNWDP (SEQ ID NO: 2888)
1028H06	1190	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-121	DFSPYDILTYGLPYATGRNWDP (SEQ ID NO: 2843)
1028H09	1191	140-250	162-175	191-197	230-239	1-124	26-35	50-66	101-113	EIDDLTGYMDV (SEQ ID NO: 2905)
1029A10	1192	139-246	160-170	186-192	225-235	1-123	26-35	50-65	98-112	MNYDILTGLVNWDP (SEQ ID NO: 2786)
1029A12	1193	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110	RDILTGYDS (SEQ ID NO: 2933)
1029B11	1194	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1029C08	1195	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDILTYGVGVGRMDV (SEQ ID NO: 2171)
1029E10	1196	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLITRSLAGPLDN (SEQ ID NO: 2751)
1029F08	1197	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLITRSLAGPLDN (SEQ ID NO: 2751)
1029G08	1198	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	GYDILTYQSDAFDI (SEQ ID NO: 2927)
1030A02	1199	142-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	TERFGAKDVTARWGMVDV (SEQ ID NO: 2874)
1030A03	1200	140-253	163-175	191-197	230-242	1-124	26-35	50-66	99-113	ENYDILTYGNFFDY (SEQ ID NO: 2737)
1030A04	1201	140-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	ROYDILTYGVGGFDY (SEQ ID NO: 2958)
1030A05	1202	140-249	163-175	191-197	230-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030A09	1203	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030A12	1204	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030B06	1205	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030B08	1206	140-247	163-173	189-195	228-236	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030B10	1207	141-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114	ELGHREGGWYSPNV (SEQ ID NO: 2838)
1030C03	1208	139-252	162-175	191-197	230-241	1-123	26-35	50-66	99-112	DPGNTDILTYYYYYGMDV (SEQ ID NO: 2935)
1030C06	1209	146-256	169-182	198-204	237-245	1-130	26-35	50-68	101-119	SGPGWDP (SEQ ID NO: 2870)
1030C08	1210	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030C09	1211	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030C10	1212	140-250	162-175	191-197	230-239	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030C11	1213	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030C12	1214	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	SGPGWDP (SEQ ID NO: 2870)
1030D07	1215	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030D12	1216	140-251	163-175	191-197	230-240	1-123	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030E02	1217	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)



1030E05	1218	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030E07	1219	140-251	165-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030E08	1220	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030E09	1221	140-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030E10	1222	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1030F02	1223	141-252	164-176	192-198	231-241	1-125	26-37	52-67	100-114	AGYDILLGYPFEDS (SEQ ID NO: 2757)
1030F05	1224	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030F06	1225	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1030F08	1226	140-254	163-176	192-198	231-243	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030F09	1227	140-253	164-176	192-198	231-242	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030F11	1228	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1030F12	1229	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	DNYDILTGYSRRDP (SEQ ID NO: 2942)
1030G03	1230	140-256	163-176	192-202	237-245	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030G07	1231	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1030G09	1232	140-251	164-174	190-196	229-240	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1030H05	1233	145-255	168-181	197-203	236-244	1-129	26-35	50-66	99-118	DRGNNVILTGYYFHHGVDV (SEQ ID NO: 2914)
1030H06	1234	146-258	170-182	198-204	239-247	1-130	26-37	52-69	102-119	ATKSYDILTRMYYHYMDV (SEQ ID NO: 2748)
1030H10	1235	140-253	163-176	192-198	231-242	1-124	26-35	50-66	99-113	DNYDILTGYSRRDP (SEQ ID NO: 2942)
1030H11	1236	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGISVGATTGALDM (SEQ ID NO: 2174)
1031A01	1237	137-248	160-173	189-195	228-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031A03	1238	141-251	166-176	192-198	231-240	1-125	26-35	50-66	99-114	PYYDPLTAYTFQVFGN (SEQ ID NO: 2806)
1031A08	1239	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	GREDTDKVKPWDRYYHYMDV (SEQ ID NO: 2809)
1031A12	1240	146-257	169-181	197-203	236-246	1-130	26-35	50-66	99-119	GLGHTSDS (SEQ ID NO: 2871)
1031B03	1241	136-246	159-172	188-194	227-235	1-120	26-35	50-68	101-109	AKGYDSSGASVDY (SEQ ID NO: 2809)
1031B06	1242	142-253	165-177	193-199	232-242	1-126	26-35	50-66	99-113	GREDTDKVKPWDRYYHYMDV (SEQ ID NO: 2809)
1031B07	1243	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	GREDTDKVKPWDRYYHYMDV (SEQ ID NO: 2159)
1031B08	1244	147-258	171-183	199-205	238-249	1-131	26-35	50-66	99-120	SNPKWYDALTGHSYHSAAMDV (SEQ ID NO: 2840)
1031B09	1245	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SNPKWYDALTGHSYHSAAMDV (SEQ ID NO: 2840)
1031B11	1246	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031B12	1247	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	GREDTDKVKPWDRYYHYMDV (SEQ ID NO: 2809)
1031C01	1248	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031C02	1249	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	PFYDILTSYVFOYEDH (SEQ ID NO: 2137)
1031C04	1250	147-260	171-183	199-205	238-249	1-131	26-35	50-66	99-120	GREDTDKVKPWDRYYHYMDV (SEQ ID NO: 2813)
1031C08	1251	137-248	161-171	187-193	226-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031C11	1252	147-257	171-181	197-203	236-246	1-131	26-35	50-66	99-120	GREDTDKVKPWDRYYHYMDV (SEQ ID NO: 2809)
1031D01	1253	145-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118	AATTSQKHKNYAYFYGMDV (SEQ ID NO: 2131)

1031D04	1254	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031D06	1255	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	GREDTDKVKLWDRYHHYYMDV (SEQ ID NO: 2807)
1031D08	1256	144-257	167-180	196-202	235-246	1-128	26-35	50-66	99-117	VRPKLYRFDWLSRFAEDL (SEQ ID NO: 2820)
1031D09	1257	137-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031D11	1258	147-256	171-181	197-203	236-245	1-131	26-35	50-66	99-117	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2165)
1031D12	1259	144-254	168-178	194-200	233-243	1-128	26-35	50-66	99-120	DKAHGEYGRDYHHYYMDV (SEQ ID NO: 2735)
1031E01	1260	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2159)
1031E05	1261	147-257	171-181	197-203	236-246	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2159)
1031E07	1262	147-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2159)
1031E09	1263	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	GREDTDKVKPDRYHHYYMDV (SEQ ID NO: 2809)
1031E10	1264	137-246	162-173	189-195	228-235	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031E11	1265	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2165)
1031F01	1266	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2159)
1031F04	1267	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031F06	1268	137-246	162-172	188-194	227-235	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031F10	1269	135-247	159-171	187-193	226-236	1-119	26-35	50-66	99-108	DTVRSGGMDV (SEQ ID NO: 2804)
1031F11	1270	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	GREDTDKVKPDRYHHYYMDV (SEQ ID NO: 2809)
1031F12	1271	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	DKAHGEYGRDYHHYYMDV (SEQ ID NO: 2735)
1031G01	1272	137-249	160-172	188-194	227-238	1-121	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031G03	1273	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2159)
1031G05	1274	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	GREDTDKVKPDRYHHYYMDV (SEQ ID NO: 2809)
1031G06	1275	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2816)
1031G07	1276	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-118	AATTSQKHKNAYFYGYMDV (SEQ ID NO: 2809)
1031G09	1277	147-259	171-183	199-205	238-248	1-131	26-35	50-66	99-110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031G12	1278	147-263	170-183	199-209	244-252	1-131	26-35	50-66	99-115	AKGYDSSGASDFVDV (SEQ ID NO: 2871)
1031H01	1279	145-256	168-180	196-202	235-245	1-129	26-35	50-66	99-120	GREDTDKVKPDRYHHYYMDV (SEQ ID NO: 2809)
1031H02	1280	137-250	160-173	189-195	228-239	1-121	26-35	50-66	99-117	DKAHGEYGRDYHHYYMDV (SEQ ID NO: 2735)
1031H03	1281	142-255	165-178	194-200	233-244	1-126	26-35	50-66	99-110	DTVRSGGMDV (SEQ ID NO: 2804)
1031H06	1282	147-260	170-183	199-205	238-249	1-131	26-35	50-66	99-120	SPPKWYDALTGDSSTHSAAMDV (SEQ ID NO: 2159)
1031H09	1283	144-257	167-179	195-201	234-244	1-128	26-35	50-66	99-117	DKAHGEYGRDYHHYYMDV (SEQ ID NO: 2735)
1031H10	1284	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	DKAHGEYGRDYHHYYMDV (SEQ ID NO: 2735)
1031H11	1285	147-256	166-179	195-201	234-245	1-127	26-35	50-66	99-116	DRTGYDLRYGGYFDF (SEQ ID NO: 2931)
1033A08	1286	135-246	158-170	186-192	225-235	1-119	26-35	50-66	99-108	DTVRSGGMDV (SEQ ID NO: 2804)
1033B11	1287	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	DRYDLTGYYYGYMDV (SEQ ID NO: 2129)
1033C01	1288	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	DRYDLTGYYYGYMDV (SEQ ID NO: 2129)
	1289	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)

1033C08	1290	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	EMGYDILTGYYLNTMDV (SEQ ID NO: 2862)
1033D02	1291	138-245	161-171	187-193	226-234	1-122	26-35	50-66	99-111	GXYDILTGYYMDV (SEQ ID NO: 2781)
1033D03	1292	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1033D05	1293	141-251	163-176	192-198	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1033D11	1294	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-117	KRDLTGYYVEGMDV (SEQ ID NO: 2869)
1033D12	1295	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	GGHYDILTGYYMAVGFDI (SEQ ID NO: 2962)
1033E01	1296	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-112	DIDAKLAADAFDI (SEQ ID NO: 2794)
1033E06	1297	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-112	ATHDPLTGYSFDGFDI (SEQ ID NO: 2780)
1033E11	1298	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116	HKRSCTSSCRDAFDI (SEQ ID NO: 2770)
1033F02	1299	142-249	163-173	189-195	225-235	1-126	26-35	50-66	99-115	EMGYDILTGYYLNTMDV (SEQ ID NO: 2862)
1033F03	1300	139-246	160-170	186-192	228-238	1-123	26-35	50-66	99-112	EGAADYLGQYFQD (SEQ ID NO: 2768)
1033F08	1301	145-256	167-179	195-201	234-245	1-129	26-35	50-66	99-118	KQVYDILTGYYYYGMDV (SEQ ID NO: 2767)
1033F10	1302	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVKNYDILTRSLAGPLDN (SEQ ID NO: 2751)
1033F12	1303	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	DIDIGDDDS (SEQ ID NO: 2954)
1033G01	1304	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYTGNGAFDI (SEQ ID NO: 2158)
1033G03	1305	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	PGQVTLVRGAETDAFI (SEQ ID NO: 2925)
1033G08	1306	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1033H04	1307	140-247	161-171	187-193	226-236	1-124	25-34	49-65	98-113	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1037A05	1308	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	SRDLTLFPHYGMDV (SEQ ID NO: 2133)
1037B03	1309	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114	SHYDILTRLNYYWYFDL (SEQ ID NO: 2950)
1037B04	1310	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117	DPGYDILTGYYFHRGMDV (SEQ ID NO: 2922)
1037C04	1311	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115	ENGVDILTGTFYGMVDV (SEQ ID NO: 2752)
1037C06	1312	141-249	163-173	189-195	228-238	1-125	26-35	50-66	99-114	LYDILTGYYRWDAFDI (SEQ ID NO: 2882)
1037C08	1313	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
1037D11	1314	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	SQWLEHDVFI (SEQ ID NO: 2864)
1037E06	1315	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DRRDYDILTRYYYYGMDV (SEQ ID NO: 2928)
1037F04	1316	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	KQRGDYDLTGYYQLGYAFDI (SEQ ID NO: 2808)
1037G01	1317	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SHYDILTRLNYYWYFDL (SEQ ID NO: 2950)
1037G03	1318	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	DILGYSYDILTRALNENYGMVDV (SEQ ID NO: 2963)
1037G10	1319	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	DYDIDILTKLPGYGMVDV (SEQ ID NO: 2975)
1042A07	1320	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117	VSPSYDILTGYYLPHAFDV (SEQ ID NO: 2849)
1042A10	1321	142-249	165-175	191-197	230-238	1-126	26-35	50-65	98-115	GPYYDILTGYYVNWFPD (SEQ ID NO: 2801)
1042B03	1322	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	DIDILTGYYVLGMDV (SEQ ID NO: 2924)
1042B12	1323	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SHYDILTRLNYYWYFDL (SEQ ID NO: 2166)
1042D01	1324	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	QQWLPYDAFDI (SEQ ID NO: 2839)
1042D03	1325	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113	AYYDILTGYYFEDI (SEQ ID NO: 2873)

1042D10	1326	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115	ERADYDLITGYFFYGMVDY (SEQ ID NO: 2802)
1042E10	1327	147-257	169-182	198-204	237-246	1-131	26-37	52-69	102-120	ERPYYDLITGYTYTGMDV (SEQ ID NO: 2798)
1042E11	1328	140-242	161-177	187-193	226-236	1-124	26-35	50-66	99-113	DEYDILTGILQGMVDY (SEQ ID NO: 2883)
1042F08	1329	140-242	161-177	187-193	232-241	1-126	26-37	52-67	100-115	GGYDILTGYPHAFDI (SEQ ID NO: 2738)
1042F12	1330	140-247	161-177	188-194	226-236	1-124	26-35	50-66	99-113	DGYDILTGYYFGMDY (SEQ ID NO: 2976)
1042G08	1331	141-248	162-172	187-194	227-237	1-125	26-35	50-66	99-114	EHYDILTGYSLGMVDY (SEQ ID NO: 2907)
1042G10	1332	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SHYDILTGLNYYWFDL (SEQ ID NO: 2166)
1042H03	1333	143-253	165-178	194-200	233-242	1-127	26-35	50-66	98-116	GSLYYDILTGYYIGNAFDI (SEQ ID NO: 2759)
1043A03	1334	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGYDILTGFGYYYGMVDY (SEQ ID NO: 2899)
1043B02	1335	142-249	163-173	189-195	228-238	1-126	26-35	50-65	98-115	GGYYDILTGVLYYYGMVDY (SEQ ID NO: 2744)
1043B03	1336	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1043B06	1337	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DQYDILTGYYHIDYMDY (SEQ ID NO: 2828)
1043B07	1338	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1043B09	1339	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1043D11	1340	144-254	166-179	195-201	234-243	1-128	26-35	50-65	98-116	HVRDYDILTGYYRGHFDY (SEQ ID NO: 2777)
1043E05	1341	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-117	EVRNYDILTRSYPAGPLDN (SEQ ID NO: 2751)
1043F01	1342	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-116	TESNYDILTGYYWPSMDY (SEQ ID NO: 2940)
1043F04	1343	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1043F12	1344	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1043H07	1345	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	TESNYDILTGYYWPSMDY (SEQ ID NO: 2940)
1044A11	1346	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1044B11	1347	139-249	161-173	189-195	228-238	1-123	26-35	50-68	101-117	APYDILTGYSDDYGMVDY (SEQ ID NO: 2968)
1044C09	1348	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-112	DSDARI AALDAFDI (SEQ ID NO: 2978)
1044C10	1349	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-113	QGFGLPNYYHMDY (SEQ ID NO: 2943)
1044D03	1350	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-116	DIKRYNSNPYYDYMDY (SEQ ID NO: 2726)
1044D09	1351	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DKQYYDILTGDPVEGGMVDY (SEQ ID NO: 2889)
1044E07	1352	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1044E11	1353	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	AGSILVTYGTDV (SEQ ID NO: 2825)
1044F07	1354	147-257	169-182	198-204	237-246	1-131	26-35	50-66	99-116	SDDYDILTGNYVGSLLDY (SEQ ID NO: 2758)
1044G02	1355	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-120	DGRJSDYDILGYDYARDYGMVDY (SEQ ID NO: 2912)
1044G07	1356	149-259	171-184	200-206	239-248	1-133	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1044H01	1357	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-122	DQNHDPDILTGYYPTGLEKN (SEQ ID NO: 2845)
1050A01	1358	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-117	EVRNYDILTRSYPAGPLDN (SEQ ID NO: 2751)
1050B12	1359	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	DMGYDILTGYYGAFDI (SEQ ID NO: 2946)
1050C06	1360	140-248	165-175	191-197	230-237	1-125	26-35	50-66	99-114	DYYDVLTGSLDGMVDY (SEQ ID NO: 2829)
1050C08	1361	141-253	164-177	193-199	232-242	1-125	26-37	52-67	98-113	DHYDVLTGSLYQAQFDY (SEQ ID NO: 2728)
									100-114	GRYDVLTGLYRNFDY (SEQ ID NO: 2731)

1050E01	1362	140-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	GHYDILTYGFFGFDY (SEQ ID NO: 2886)
1050E10	1363	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	DMKYVYKALDV (SEQ ID NO: 2823)
1050H08	1364	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	DLRYDILTYGHDADF (SEQ ID NO: 2890)
1051A04	1365	147-238	170-183	199-205	238-247	1-131	26-35	50-66	99-120	SPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
1051A08	1366	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	HRKARVVPVPGAMDV (SEQ ID NO: 2930)
1051A12	1367	143-250	164-174	196-199	229-239	1-127	26-35	50-66	99-116	DCGSYDILTYGIDNMDV (SEQ ID NO: 2154)
1051B08	1368	142-253	165-177	193-199	232-242	1-126	26-36	51-67	100-115	RSNIVVTIAPDAPDL (SEQ ID NO: 2785)
1051C06	1369	135-246	158-170	186-192	225-235	1-119	26-35	50-66	99-108	DTVRSGGMDV (SEQ ID NO: 2804)
1051G12	1370	143-250	164-174	196-199	229-239	1-127	26-35	50-66	99-116	DCGSYDILTYGIDNMDV (SEQ ID NO: 2154)
1055A05	1371	133-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	SCPGWFDP (SEQ ID NO: 2870)
1055A11	1372	133-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	SCPGWFDP (SEQ ID NO: 2870)
1061A03	1373	140-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSVGAITGALDM (SEQ ID NO: 2852)
1061A04	1374	141-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114	GDYDILTYGPAECFCI (SEQ ID NO: 2854)
1061A08	1375	140-253	164-176	192-198	233-242	1-124	26-35	50-66	99-113	DNYDILTYSRFP (SEQ ID NO: 2942)
1061A09	1376	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1061A10	1377	140-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1061B07	1378	140-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1061B09	1379	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTYGIGNAGFDI (SEQ ID NO: 2158)
1061C12	1380	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1061C12	1381	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	TYDILTYGFFHDY (SEQ ID NO: 2788)
1061D01	1382	137-247	159-172	188-194	227-236	1-121	26-35	50-66	101-110	GPVGINDY (SEQ ID NO: 2749)
1061D03	1383	141-251	163-176	192-198	231-240	1-124	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1061D04	1384	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	AVLRYASGLQGAFDI (SEQ ID NO: 2970)
1061D07	1385	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	VSGYNSGFHSDMDV (SEQ ID NO: 2732)
1061D09	1386	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	LNLEKTVVRGFGYDL (SEQ ID NO: 2952)
1061D10	1387	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	DHYDILTGLYYYGMDV (SEQ ID NO: 2760)
1061E01	1388	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	LNLEKTVVRGFGYDL (SEQ ID NO: 2952)
1061E05	1389	142-251	163-175	191-197	230-240	1-126	26-35	50-66	99-115	GGLVWFSGSYGMDV (SEQ ID NO: 2787)
1061E09	1390	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1061E12	1391	133-240	154-164	180-186	219-229	1-117	26-35	50-66	99-106	SRQLFDS (SEQ ID NO: 2842)
1061F01	1392	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	DYDILTYGIRGLDADF (SEQ ID NO: 2887)
1061F09	1393	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	DSDAALDAFDI (SEQ ID NO: 2978)
1061F10	1394	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118	ESYDILTYGYYVHYGMDV (SEQ ID NO: 2743)
1061F11	1395	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2949)
1061G01	1396	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1061G03	1397	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDILTGLFLPYDMDL (SEQ ID NO: 2771)

1398	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRYDLITRSTYLAGPLDN (SEQ ID NO: 2751)
1399	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	EGSYDLITGVYGVGRMDV (SEQ ID NO: 2171)
1400	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110	RDLITGFYDS (SEQ ID NO: 2933)
1401	142-252	164-177	193-199	232-241	1-126	26-37	52-67	100-115	ATYDPLTGYSGDFGDI (SEQ ID NO: 2153)
1402	142-249	163-175	189-195	228-238	1-126	26-35	50-68	101-115	DFYDLITGYOHGMDV (SEQ ID NO: 2919)
1403	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	HSKEYNNWYALDY (SEQ ID NO: 2754)
1404	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	TRMDVLTYYSDY (SEQ ID NO: 2750)
1405	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-111	AFEDYDLITGYHHADPI (SEQ ID NO: 2911)
1406	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-117	PSYHYMDV (SEQ ID NO: 2740)
1407	141-251	167-180	196-202	235-244	1-129	26-35	50-66	99-118	VNADYDLITGYPRDYGYMDV (SEQ ID NO: 2819)
1408	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFGDI (SEQ ID NO: 2153)
1409	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	EDATYYDLITGYMGSGMDV (SEQ ID NO: 2763)
1410	143-250	166-176	192-198	231-239	1-127	26-35	50-66	99-116	ETRKYSPPNYNYMDV (SEQ ID NO: 2736)
1411	140-251	162-174	190-196	229-240	1-124	26-35	50-66	99-113	RKYDYLITGYSGRFP (SEQ ID NO: 2725)
1412	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGYDILITLTVSYNGMDV (SEQ ID NO: 2775)
1413	140-250	162-175	191-197	230-239	1-124	26-35	50-65	98-113	GERDILITGYLLDGMVD (SEQ ID NO: 2948)
1414	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113	ERGSYSSGYSGAFDV (SEQ ID NO: 2898)
1415	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	ESGSYSGRSDYYGMDV (SEQ ID NO: 2836)
1416	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118	DRGVGYDLITGRTYYGMDV (SEQ ID NO: 2836)
1417	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFGDI (SEQ ID NO: 2153)
1418	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DVSGHDLITGYRYFDV (SEQ ID NO: 2795)
1419	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-112	GOKNYVSSGYLHH (SEQ ID NO: 2916)
1420	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113	GQYDILITGYSHFDY (SEQ ID NO: 2908)
1421	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	AYDYDLITGYSYFDY (SEQ ID NO: 2885)
1422	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1423	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1424	135-242	156-168	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1425	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	GQYDILITGYTGAFDI (SEQ ID NO: 2824)
1426	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	SKDLLPPHYGMDV (SEQ ID NO: 2133)
1427	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	GYYEYDLITGYNELGAFDI (SEQ ID NO: 2851)
1428	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGYEYDLITGYNYQYGMVD (SEQ ID NO: 2915)
1429	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1430	135-245	157-169	183-191	224-234	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1431	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DRGYDLITGYYYGMDV (SEQ ID NO: 2876)
1432	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	EVRYDILITGYYSYMDV (SEQ ID NO: 2778)
1433	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)

1066B08	1434	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1066B10	1435	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	GLYFEDTNYRHGDAFDI (SEQ ID NO: 2790)
1066C02	1436	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-114	GMGDHYGMDV (SEQ ID NO: 2161)
1066C12	1437	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-118	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1066C12	1438	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-113	GMGDHYGMDV (SEQ ID NO: 2161)
1066D06	1439	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-118	ENYDELIGYGAEDI (SEQ ID NO: 2772)
1066D08	1440	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	HSKEYNNWYALDY (SEQ ID NO: 2754)
1066D11	1441	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	ERSQDFELTGVDRYHPNDV (SEQ ID NO: 2956)
1066D12	1442	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	EGAADELNGVYQFH (SEQ ID NO: 2815)
1066E12	1443	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1066E16	1444	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1066G05	1445	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	GLYFEDTNYRHGDAFDI (SEQ ID NO: 2790)
1066G08	1446	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	VYDILTGHPITYGMDV (SEQ ID NO: 2791)
1066G10	1447	144-254	166-178	194-200	233-243	1-128	26-35	50-66	101-117	GYDILTGHWDDAFDI (SEQ ID NO: 2872)
1066H12	1448	143-254	165-177	193-199	232-243	1-127	26-35	50-66	99-116	ESTYDILTGSHYDGLDV (SEQ ID NO: 2822)
1066H14	1449	143-253	165-178	194-200	233-242	1-127	26-35	50-66	98-116	DRLHYDILTGHTDDAFDI (SEQ ID NO: 2885)
1067A07	1450	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	VLTYDILTGXYREDAFDM (SEQ ID NO: 2939)
1067A11	1451	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1067B08	1452	149-259	171-184	200-206	239-248	1-133	26-35	50-66	99-122	DRGASNYDILTGYYAPAGVAFDI (SEQ ID NO: 2969)
1067C08	1453	148-258	170-183	199-205	238-247	1-132	26-37	52-69	102-121	EGAHYDILTGSHYHYGMDV (SEQ ID NO: 2747)
1067C09	1454	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	ETRKYTSSPPYNYGMDV (SEQ ID NO: 2756)
1067D07	1455	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067E01	1456	140-248	164-174	190-196	229-238	1-124	26-35	50-66	99-113	DQHDILTGYYGMDV (SEQ ID NO: 2921)
1067E06	1457	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1067E07	1458	150-260	172-184	200-206	239-249	1-134	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1067E11	1459	141-251	163-176	192-198	231-240	1-125	26-35	50-66	100-123	DYPGSEYDILTGLEGYYGMDV (SEQ ID NO: 2926)
1067G03	1460	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1067G05	1461	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ARRVGVLGGKNAFI (SEQ ID NO: 2765)
1067G12	1462	141-252	163-176	192-198	231-241	1-125	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1067H05	1463	146-256	168-180	196-202	235-245	1-130	26-35	50-66	101-119	EGTYDILTGYYPLGYFDY (SEQ ID NO: 2936)
1067H06	1464	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1068C09	1465	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GSSQNFYGMDV (SEQ ID NO: 2884)
1068G03	1466	143-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	GTGYDILTGYYMGSAFDQ (SEQ ID NO: 2800)
1068G04	1467	142-252	165-178	194-200	233-241	1-126	26-35	50-66	99-115	GVVWVAYGDNVGYGHDV (SEQ ID NO: 2937)
1068G07	1468	140-251	164-174	190-196	229-240	1-124	26-35	50-66	99-113	HDYIMTAAHYTYS (SEQ ID NO: 2909)
1068G08	1469	143-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	GIGYDILLTGTYTGSPLDY (SEQ ID NO: 2846)

1070R07	1470	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	DFYDLTGYHDAFDI (SEQ ID NO: 2910)
1070G05	1471	140-250	162-175	191-197	230-239	1-124	26-35	50-66	101-113	DVDDLTGYSWDY (SEQ ID NO: 2867)
1070H02	1472	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDLTGYGYGFDY (SEQ ID NO: 2179)
1071A01	1473	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	AAYPDLTGYSGDFDI (SEQ ID NO: 2783)
1071B03	1474	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DMHYDLTGYVYTLAEDM (SEQ ID NO: 2917)
1071B08	1475	142-252	166-176	192-198	231-241	1-126	27-36	51-67	100-115	GGYDLTGYPAEFHP (SEQ ID NO: 2764)
1071E01	1476	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	DFGVDGYRPDY (SEQ ID NO: 2777)
1071F11	1477	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	SSNPYGLDV (SEQ ID NO: 2957)
1071G11	1478	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO: 2153)
1071H08	1479	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO: 2153)
1074A02	1480	141-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	DDRDLTNYLYEYFQH (SEQ ID NO: 2868)
1074A08	1481	147-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120	SSPKWYDALTGSSYHSAEDV (SEQ ID NO: 2165)
1074D10	1482	144-253	168-178	194-200	233-242	1-128	26-35	50-66	99-117	DKTLGDLQVLAAYYYDMDY (SEQ ID NO: 2776)
1074E01	1483	144-255	168-178	194-200	233-244	1-128	26-35	50-66	99-117	LGRTSRDLTGYHYNNMDV (SEQ ID NO: 2944)
1074E02	1484	140-250	164-174	190-196	229-239	1-124	26-35	50-66	99-113	DOYDLTGSLYYFDS (SEQ ID NO: 2803)
1074E08	1485	143-259	166-179	195-205	240-248	1-127	26-35	50-66	99-116	GTGYDLTGYVMGSAFDQ (SEQ ID NO: 2800)
1074F12	1486	140-250	164-174	190-196	229-239	1-124	26-35	50-66	99-113	DRADLTGYNDADF (SEQ ID NO: 2739)
1074H06	1487	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO: 2735)
1074H07	1488	143-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GTGYDLTGYVMGSAFDQ (SEQ ID NO: 2800)
1074H08	1489	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	VSNDLTGWGGYNNWFD (SEQ ID NO: 2955)
1075A07	1490	143-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GTGYDLTGYVMGSAFDQ (SEQ ID NO: 2800)
1075B01	1491	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DOGRYLDL (SEQ ID NO: 2175)
1075B04	1492	133-247	156-169	185-191	224-236	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075B06	1493	140-252	163-175	191-197	230-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1075B08	1494	143-257	166-179	195-201	234-246	1-127	26-35	50-66	99-116	GTGYDLTGYVMGSAFDQ (SEQ ID NO: 2800)
1075B09	1495	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	TYVDLTGYVAEYFQH (SEQ ID NO: 2932)
1075B12	1496	140-251	163-176	192-198	231-240	1-124	26-35	50-66	99-113	SDYDLTGYVMYPAV (SEQ ID NO: 2812)
1075C01	1497	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	GREDTKVKPWDRYPHYMMDV (SEQ ID NO: 2835)
1075C05	1498	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075D05	1499	143-253	168-179	195-201	234-242	1-125	26-35	50-66	99-116	GTGYDLTGYVMGSAFDQ (SEQ ID NO: 2837)
1075D07	1500	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	STYDILTGYVHTPLDY (SEQ ID NO: 2853)
1075D08	1501	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1075E01	1502	143-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GTGYDLTGYVMGSAFDQ (SEQ ID NO: 2800)
1075E03	1503	148-261	172-184	200-206	239-250	1-132	28-37	52-68	101-121	GGGYDLTGYSPLYYGLDV (SEQ ID NO: 2865)
1075E04	1504	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GRGYDLTGYTGTSPLDY (SEQ ID NO: 2881)
1075E05	1505	140-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)



1075E10	1506	140-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELG1SVGATTGALDM (SEQ ID NO: 2174)
1075E11	1507	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	SGRGWDFP (SEQ ID NO: 2870)
1075E12	1508	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	TRFGAKDVTARWGMVDV (SEQ ID NO: 2879)
1075F02	1509	144-254	168-178	194-200	233-242	1-128	26-35	50-66	99-117	EQGYDLTGYWPGWDFP (SEQ ID NO: 2934)
1075F04	1510	141-251	164-176	192-198	231-240	1-125	26-37	52-67	100-114	AGYDLTGYVPYFDS (SEQ ID NO: 2757)
1075F06	1511	144-254	168-178	194-200	233-243	1-128	26-35	50-66	99-117	GRNYDELGTGNFNLGLDY (SEQ ID NO: 2830)
1075F07	1512	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	ENYDSLGTYYNYPDY (SEQ ID NO: 2971)
1075F08	1513	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQKRAQDI (SEQ ID NO: 2779)
1075F09	1514	145-257	169-181	197-203	236-246	1-129	26-35	50-66	99-118	LKAPYDLTGYHLPKWFDT (SEQ ID NO: 2953)
1075F10	1515	133-243	157-167	183-189	222-232	1-117	26-35	50-66	99-116	DQGRYLDL (SEQ ID NO: 2175)
1075F11	1516	133-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075G05	1517	140-252	163-175	191-197	230-241	1-124	26-34	49-65	98-113	ELG1SVGATTGALDM (SEQ ID NO: 2174)
1075G07	1518	140-252	163-175	191-197	230-241	1-124	26-35	50-66	99-113	GRYYDMLTRGGYFDY (SEQ ID NO: 2858)
1075G08	1519	140-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	RQYDLTGYTGGFDY (SEQ ID NO: 2958)
1075G11	1520	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	TDYDLTGYPMGYFDP (SEQ ID NO: 2173)
1075G12	1521	133-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075H02	1522	143-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	GTGYDLTGYMGSAFDQ (SEQ ID NO: 2800)
1075H03	1523	133-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075H06	1524	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075H08	1525	143-254	166-179	195-201	234-243	1-127	26-35	50-66	99-116	GSYDLTGYFTGSPLDY (SEQ ID NO: 2766)
1076A01	1526	142-253	166-176	192-198	231-242	1-126	26-35	50-66	99-115	DRRRDLTGYYLDAFDS (SEQ ID NO: 2878)
1076A03	1527	135-247	159-171	187-193	226-236	1-119	26-35	50-68	101-108	GYDTANQY (SEQ ID NO: 2951)
1076A06	1528	133-245	156-168	184-190	223-234	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1076A07	1529	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-102	DQGRYLDL (SEQ ID NO: 2175)
1076A08	1530	142-253	166-176	192-198	231-242	1-126	26-35	50-66	99-115	DRRDLTGSNFGDQ (SEQ ID NO: 2913)
1076B01	1531	143-257	167-179	195-201	236-246	1-127	26-35	50-66	99-116	MGHYDLTGYRHYGMVDV (SEQ ID NO: 2831)
1076B03	1532	133-245	156-169	183-191	224-234	1-117	26-35	50-66	99-106	GSYDLTGYFTGSPLDY (SEQ ID NO: 2766)
1076B07	1533	133-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1076B08	1534	141-252	166-179	193-199	232-241	1-125	26-35	50-66	99-114	PYDPLTAYTFQYFGN (SEQ ID NO: 2806)
1076C04	1535	140-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELG1SVGATTGALDM (SEQ ID NO: 2174)
1076C10	1536	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	GRYYDMLTRGGYFDY (SEQ ID NO: 2858)
1076D01	1537	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	LDYDLTGYVPYGFDS (SEQ ID NO: 2799)
1076D08	1538	140-251	163-175	191-197	230-240	1-124	26-37	52-67	100-113	REYDLTGYSAFDS (SEQ ID NO: 2756)
1076D11	1539	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GTGYDLTGYMGSAFDQ (SEQ ID NO: 2800)
1076D12	1540	140-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELG1SVGATTGALDM (SEQ ID NO: 2174)
1076E04	1541	143-252	167-177	193-199	232-241	1-127	26-35	50-66	99-116	GTGYDLTGYMGSAFDQ (SEQ ID NO: 2800)

1076E07	1542	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	EYDVLTLGLFYMDY (SEQ ID NO: 2841)
1076E09	1543	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	DDRDILNYYLEYFQH (SEQ ID NO: 2868)
1076E11	1544	143-254	166-179	195-201	234-243	1-127	26-35	50-66	99-116	GTGYDILTGYMGSAFDQ (SEQ ID NO: 2800)
1076F01	1545	143-253	166-178	194-199	232-242	1-127	26-35	50-66	99-116	GTGYDILTGYMGSAFDQ (SEQ ID NO: 2800)
1076F03	1546	140-251	163-175	191-197	230-240	1-124	26-36	51-66	99-113	GDYDVLTYGLRKLIDY (SEQ ID NO: 2742)
1076F04	1547	133-245	157-169	185-191	224-234	1-117	26-35	50-66	99-106	DQGRYDL (SEQ ID NO: 2175)
1076F08	1548	140-250	164-174	190-196	229-239	1-124	26-36	51-66	99-113	VHYDILTYGLWAFDI (SEQ ID NO: 2730)
1076F10	1549	140-252	163-175	191-197	230-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1076G09	1550	133-245	156-168	184-190	223-234	1-117	26-35	50-66	99-106	DQGRYDL (SEQ ID NO: 2175)
1076G10	1551	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	GRYDMLTRGGYFDY (SEQ ID NO: 2858)
1076G11	1552	143-259	166-179	195-205	240-248	1-127	26-35	50-66	99-116	GTGYDILTGYMGSAFDQ (SEQ ID NO: 2800)
1076G12	1553	146-257	169-181	197-203	236-246	1-130	26-35	50-66	99-119	NGYDILTGYLWDYGYMDY (SEQ ID NO: 2769)
1076H02	1554	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	ENYDSLTYGYNFYD (SEQ ID NO: 2971)
1076H04	1555	141-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114	THYDILTYGYSHPLDY (SEQ ID NO: 2863)
1076H05	1556	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1076H06	1557	140-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	VHYDILTYGWGAFDY (SEQ ID NO: 2837)
1076H09	1558	143-256	166-179	195-201	234-245	1-127	26-35	50-66	99-116	GSQYDILTYGTGSPDY (SEQ ID NO: 2766)
1076H10	1559	143-256	166-179	195-201	234-245	1-127	26-35	50-66	99-116	GSQYDILTYGTGSPDY (SEQ ID NO: 2766)
1077D06	1560	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTYGNLFDDY (SEQ ID NO: 2177)
1078B04	1561	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTYGNLFDDY (SEQ ID NO: 2177)
1078E10	1562	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTYGYGGYFDY (SEQ ID NO: 2179)
1002A01-K	1563	141-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1002A01-R	1564	141-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1026C04-K	1565	141-250	164-176	192-198	231-239	1-125	26-35	50-66	99-114	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1026C04-R	1566	141-250	164-176	192-198	231-239	1-125	26-35	50-66	99-114	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1067B10	1567	149-259	171-183	199-205	238-248	1-133	26-35	50-66	99-122	DRGAPNYDILTYGYAPQAQAFDI (SEQ ID NO: 2174)
1068C06	1568	133-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	DQGRYDL (SEQ ID NO: 2175)
1075F12	1569	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYDL (SEQ ID NO: 2175)
1003C06	1570	140-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1025B09	1571	140-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1026C04	1572	140-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1026C04	1573	140-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1027B12	1574	141-250	164-174	190-196	229-239	1-125	26-34	49-65	99-114	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1030A10	1575	140-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1064C04	1576	147-257	169-182	198-204	237-246	1-131	26-35	50-66	99-120	SGRYSYDILTYGYARDYGYMDY (SEQ ID NO: 2188)
1064C07	1577	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	DESLTYGTFVDY (SEQ ID NO: 2178)

1063D04	1578	144-254	166-179	195-201	234-243	1-128	26-36	51-66	99-117	GKGYDILTYGYRDNWEDP (SEQ ID NO: 2181)
1065D08	1579	147-257	169-182	198-204	237-246	1-131	26-35	50-66	99-120	TPSSYDILTYGYHYFTYMDV (SEQ ID NO: 2189)
1065F08	1580	135-242	158-168	184-190	223-231	1-119	26-35	50-66	99-108	EKSAAGYFDY (SEQ ID NO: 2190)
1066F08	1581	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ENYSLTYGYGAFDI (SEQ ID NO: 2185)
1068B04	1582	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYLDI (SEQ ID NO: 2175)
1068B08	1583	140-252	163-175	191-197	231-241	1-124	26-34	49-65	98-113	KGLSIVGATTGALDM (SEQ ID NO: 2186)
1068C08	1584	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	EGMDFNSHHYTYMDA (SEQ ID NO: 2182)
1068F03	1585	139-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	AGNEYGHTERPADY (SEQ ID NO: 2180)
1069B07	1586	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTYGYGYFDY (SEQ ID NO: 2179)
1071B03	1587	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYGSDGFDI (SEQ ID NO: 2153)
1072B09	1588	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTYGSDGFDI (SEQ ID NO: 2153)
1073F04	1589	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	SLATRPLGMDV (SEQ ID NO: 2184)
1074B12	1590	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1075A02	1591	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1075G01	1592	140-251	164-174	190-196	229-240	1-124	26-35	50-66	99-113	DHFDILTGYRRLDS (SEQ ID NO: 2187)
1078D02	1593	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTGYNLFFDY (SEQ ID NO: 2177)
1078D08	1594	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DAQSYDILTYGQSYAFDI (SEQ ID NO: 2183)
1078H08	1595	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTGYNLFFDY (SEQ ID NO: 2177)
1064A03	1596	150-257	171-181	197-203	236-246	1-134	26-35	50-66	99-123	GPSTTYDILTYGYTYPPYYTMDV (SEQ ID NO: 3014)
1064B03	1597	145-255	167-179	195-201	234-244	1-129	26-37	52-67	100-118	HVRDYDILTYGYRHHYFDY (SEQ ID NO: 2167)
1064B05	1598	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113	ERGVTAVGGDSFDL (SEQ ID NO: 2985)
1064B11	1599	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	DRGRLSSFEES (SEQ ID NO: 3033)
1064C02	1600	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	DEYDILTYGQAQYYGYMDV (SEQ ID NO: 3068)
1064C03	1601	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ERGVVAVGGDSFDL (SEQ ID NO: 2985)
1064C11	1602	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DVITYHDILTGYAGHEAFDI (SEQ ID NO: 3055)
1064C12	1603	148-255	171-181	197-203	236-244	1-132	26-37	52-69	102-121	ESGRYDILTYGSGGMDV (SEQ ID NO: 3012)
1064D03	1604	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-114	DGANYDILTYGYTYTYGYMDV (SEQ ID NO: 3072)
1064D04	1605	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	RSYDILTYGYTYGYMDV (SEQ ID NO: 3090)
1064D06	1606	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	EOSSGYLVG (SEQ ID NO: 2981)
1064D05	1607	146-256	168-180	196-202	235-245	1-130	26-37	52-67	100-119	KORGVDILTGYQLGYAFDI (SEQ ID NO: 2808)
1064E06	1608	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118	ERPGVDILTGYSSPYGMDV (SEQ ID NO: 3053)
1064F07	1609	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTYGSDGFDI (SEQ ID NO: 2153)
1064F09	1610	147-257	169-181	197-203	236-246	1-131	26-35	50-66	99-120	DTLGYDILTYGPPPPYYGYMDV (SEQ ID NO: 2988)
1064F10	1611	143-253	165-177	193-199	232-242	1-127	22-31	46-62	95-116	DTLGYDILTYGPPPPYYGYMDV (SEQ ID NO: 2988)
1064F11	1612	142-252	164-177	193-199	232-241	1-126	26-35	50-66	98-115	GRHYDILTGYNEAFDI (SEQ ID NO: 3031)
1064F11	1613	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	NYDVLTSQYYGYMDV (SEQ ID NO: 3077)

1064G04	1614	133-243	155-167	183-189	222-232	1-117	26-35	50-66	99-106	DNSGTGY (SEQ ID NO: 3084)
1064G08	1615	138-245	159-169	185-191	224-234	1-122	26-35	50-66	99-111	GGVTAAGSVYFDS (SEQ ID NO: 2990)
1064G10	1616	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	SPNGDYSYAWGLE (SEQ ID NO: 3085)
1064G11	1617	138-248	160-173	189-195	228-237	1-122	26-35	50-65	98-111	YFDGSGYVPSFYS (SEQ ID NO: 3064)
1064G12	1618	139-249	161-173	189-195	228-238	1-123	26-35	50-65	98-112	VNYDILTGLGYFDY (SEQ ID NO: 3049)
1064H03	1619	143-253	165-178	194-200	233-242	1-127	26-37	52-67	100-116	SVYDILTGPRYTDAFI (SEQ ID NO: 2989)
1064H04	1620	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	PLGTAVRGAKTDAFI (SEQ ID NO: 2929)
1064H06	1621	149-256	170-180	196-202	235-245	1-133	26-35	50-66	99-122	DGASNYDILTGYYAPQAQVAFDI (SEQ ID NO: 2969)
1065A02	1622	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A04	1623	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A06	1624	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A07	1625	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGGGYDILTGYYYYGMDV (SEQ ID NO: 2987)
1065B01	1626	145-255	167-180	196-202	235-244	1-129	26-35	50-65	98-118	WATYDILTGYYRKLKHAGFDI (SEQ ID NO: 3017)
1065B05	1627	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	SPGDDILTGYYKYFDY (SEQ ID NO: 3032)
1065B09	1628	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-119	DAGESYDILTGYYVIEGYMDV (SEQ ID NO: 2986)
1065B12	1629	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	EGAADYLNQGVFQH (SEQ ID NO: 2815)
1065C02	1630	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109	EGSWGLDLDY (SEQ ID NO: 3007)
1065C06	1631	141-253	163-175	191-197	230-242	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065C08	1632	141-250	163-176	192-198	231-239	1-125	26-35	50-66	99-114	VSGYNSGYEYSFDFDI (SEQ ID NO: 2732)
1065C10	1633	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	QGGQYDSPPLDV (SEQ ID NO: 3002)
1065D01	1634	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DRDYDILTGYSN'GMDV (SEQ ID NO: 3074)
1065D03	1635	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	APLYDILTGYYGGNDY (SEQ ID NO: 3028)
1065D05	1636	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DKDYDILTGYYRDELIDY (SEQ ID NO: 3040)
1065D06	1637	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DPNYDILTGYYYYAMDY (SEQ ID NO: 3062)
1065E01	1638	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	EPDQLLARGHMDV (SEQ ID NO: 3027)
1065E05	1639	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	AGSSILMTYGTIDV (SEQ ID NO: 2773)
1065E06	1640	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	ARGSYDILTGYYRPGDGYFDY (SEQ ID NO: 3043)
1065E08	1641	142-249	163-178	193-195	228-238	1-126	26-35	50-66	99-115	GLYFEDTNYRHRGDAFI (SEQ ID NO: 2790)
1065E09	1642	145-255	167-179	195-201	234-244	1-129	26-35	50-65	98-118	ERSYDILTGYSRKYGMDV (SEQ ID NO: 3021)
1065E12	1643	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065F04	1644	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ERGVVTA'GGDSFDL (SEQ ID NO: 2985)
1065F05	1645	140-250	162-175	191-197	230-239	1-124	26-35	50-65	98-113	RYSDAL'TGYSGLAFDY (SEQ ID NO: 3018)
1065F07	1646	145-252	166-176	192-198	231-241	1-129	26-38	53-69	102-118	GAYDILTGYYPPYGMV (SEQ ID NO: 2860)
1065F09	1647	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DYPIDVLTGRRTKNWFDP (SEQ ID NO: 3033)
1065F12	1648	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	DQVDRLLMOYNYMDA (SEQ ID NO: 3047)
1065G01	1649	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)

1065G09	1650	143-253	165-178	194-200	233-242	1-127	26-35	50-68	101-116	DAYDILTGWVYMDV (SEQ ID NO: 3030)
1065G10	1651	140-247	161-171	187-193	226-236	1-124	26-36	51-66	99-113	FRYDILTGYYMDV (SEQ ID NO: 2983)
1065H05	1652	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-111	EYDILTGYSAGFDI (SEQ ID NO: 2984)
1065H07	1653	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	TRMDVLTTRYSDP (SEQ ID NO: 2750)
1066A05	1654	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-111	AGSLMITYGTDV (SEQ ID NO: 2773)
1066A06	1655	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	EGAADYLNQGFQH (SEQ ID NO: 2815)
1066A12	1656	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DTRVIGQLWERGAFTM (SEQ ID NO: 3080)
1066B05	1657	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1066B11	1658	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	PLGITAVRGAKTDAFGI (SEQ ID NO: 2929)
1066C06	1659	141-248	166-178	194-200	233-243	1-128	26-35	50-65	98-117	GRRYDILTGYSLGRGEMDV (SEQ ID NO: 3009)
1066D02	1661	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1066D07	1662	141-248	162-172	188-194	227-237	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1066E01	1663	137-247	159-172	188-194	227-237	1-125	26-35	50-66	99-114	GPYDVLITGLSGNFDY (SEQ ID NO: 2992)
1066E03	1664	149-259	171-184	200-206	239-248	1-133	26-35	50-66	99-110	QGGQYDPPEDV (SEQ ID NO: 3001)
1066E04	1665	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-112	GEKARYDILTGYYSAWGGYYMDV (SEQ ID NO: 3045)
1066E05	1666	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-114	LNLEKTVIRGFGYDL (SEQ ID NO: 3081)
1066E07	1667	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-115	VGGYDILTGYYLRGMDV (SEQ ID NO: 2997)
1066E09	1668	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1066F01	1669	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1066F03	1670	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SPYDILTGYYVNGYDV (SEQ ID NO: 3058)
1066F04	1671	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1066F07	1672	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	VAAAGARTLGVHGMV (SEQ ID NO: 3071)
1066F08	1673	144-254	166-179	195-201	234-243	1-127	26-35	50-66	99-116	DVSGHDILTGYSRYTVD (SEQ ID NO: 2795)
1066F11	1674	142-252	164-177	193-199	232-241	1-128	26-35	50-66	99-117	SPMYDRLTGFPSTGYD (SEQ ID NO: 3036)
1066F12	1675	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-115	GAYYDILTGYYPGMDV (SEQ ID NO: 2860)
1066G06	1676	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-114	GPSSAGTTTGLGSDP (SEQ ID NO: 3005)
1066G07	1677	133-243	155-168	184-190	223-232	1-117	26-30	45-61	94-106	ETRKYTSSPPYYMDV (SEQ ID NO: 2736)
1066H02	1678	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	DQPSVGGRRHFDL (SEQ ID NO: 3054)
1067A02	1679	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-110	GMGDHYGMDV (SEQ ID NO: 2161)
1067A03	1680	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1067A06	1681	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-110	AGSLMITYGTDV (SEQ ID NO: 2773)
1067A08	1682	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-114	ATYDPLTGYSDFGDI (SEQ ID NO: 2153)
1067A10	1683	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	AGSLMITYGTDV (SEQ ID NO: 2773)
1067B03	1684	142-253	164-177	193-199	232-242	1-126	26-35	50-66	99-115	ERGVVTA'YAGDSFDL (SEQ ID NO: 2985)
1067B04	1685	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	PLGITAVRGAKTDAFGI (SEQ ID NO: 2929)

1067C03	1686	133-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	DWGHWFDP (SEQ ID NO: 2982)
1067C05	1687	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	SGSSLMTYGTDV (SEQ ID NO: 3015)
1067C07	1688	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	EPYDILTYGYSYFDY (SEQ ID NO: 3041)
1067C10	1689	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067C12	1690	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	TYDILTYGSGGAFDY (SEQ ID NO: 3024)
1067D01	1691	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	GSRVGVTPLD (SEQ ID NO: 3020)
1067D03	1692	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067D05	1693	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	ECSSGSPARQPYQYQYMDV (SEQ ID NO: 2993)
1067D06	1694	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067D09	1695	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	GAYDILTYGYPYQYMDV (SEQ ID NO: 2860)
1067D12	1696	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	QGGQYDSPLDV (SEQ ID NO: 3002)
1067E02	1697	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067E04	1698	142-252	164-176	192-198	231-241	1-126	26-35	50-66	99-115	GAYDILTYGYPYQYMDV (SEQ ID NO: 2860)
1067E05	1699	144-254	166-179	193-201	234-243	1-128	26-35	50-66	99-117	DYRNYDILTHPPYQYQYMDV (SEQ ID NO: 2996)
1067F01	1700	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	QHYDILTYGQEPFDI (SEQ ID NO: 3022)
1067F03	1701	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DQTYDILTHGYQYQYMDV (SEQ ID NO: 3087)
1067F04	1702	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	EGAADVLNGQVFQH (SEQ ID NO: 2815)
1067F08	1703	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	LGTYDILTYGRSDDY (SEQ ID NO: 3029)
1067F10	1704	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMAYGTDV (SEQ ID NO: 3016)
1067F11	1705	140-248	161-171	187-193	226-237	1-124	26-35	50-66	99-113	ENYDILTYGSGAFDI (SEQ ID NO: 2772)
1067G01	1706	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYGSDGFDI (SEQ ID NO: 2153)
1067G09	1707	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067H07	1708	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	GGLYDILTYGRPATDDAFDI (SEQ ID NO: 3035)
1068A07	1709	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	TRFGAKDVTARWGMDV (SEQ ID NO: 2979)
1068E05	1710	147-257	170-183	199-205	238-246	1-131	26-35	50-66	99-120	GREDTDKVPWDRYHYHYMDV (SEQ ID NO: 2809)
1068E08	1711	133-247	157-169	185-193	226-236	1-117	26-35	50-66	99-106	DQCRYLDL (SEQ ID NO: 2175)
1068E11	1712	140-251	163-176	192-198	231-240	1-124	26-35	50-66	99-113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1068F04	1713	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	ELGHREGGWYSPYV (SEQ ID NO: 2838)
1068G05	1714	135-245	159-169	185-191	224-234	1-119	26-35	50-66	98-108	KNMGASAAADF (SEQ ID NO: 3042)
1068G06	1715	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	YRGDPFYYYYMMV (SEQ ID NO: 2755)
1068G11	1716	146-258	169-182	198-204	237-247	1-130	26-35	50-66	99-119	ESGSHYDILTLGLVAANGFDV (SEQ ID NO: 3044)
1069A09	1717	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTYGCGYFDY (SEQ ID NO: 2179)
1069A10	1718	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTYGCGYFDY (SEQ ID NO: 2179)
1069B06	1719	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTYGCGYFDY (SEQ ID NO: 2179)
1069B09	1720	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	PYDILTYGFAFDI (SEQ ID NO: 3026)
1069B12	1721	141-248	162-172	188-194	229-237	1-125	26-35	50-66	99-114	MEYDILTYGCGYFDY (SEQ ID NO: 2179)

1069C06	1722	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	VLPHYDLTGYSONWFDP (SEQ ID NO: 3000)
1069C09	1723	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	VLPHYDLTGYSONWFDP (SEQ ID NO: 3000)
1069D03	1724	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDYDLTGYSGYGMVDV (SEQ ID NO: 2135)
1069E09	1725	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDYDLTGYSGYGMVDV (SEQ ID NO: 2135)
1069E11	1726	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	VYDYDLTGYNLFDPY (SEQ ID NO: 2177)
1069F05	1727	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1069F07	1728	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1069F12	1729	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GYDYDLTGYDAFDI (SEQ ID NO: 3051)
1069G06	1730	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDYDLTGYSGYGMVDV (SEQ ID NO: 3059)
1069G08	1731	145 - 252	166 - 176	192 - 198	231 - 241	1 - 129	26 - 35	50 - 66	99 - 118	DRLEYDYDLTGYSGYGMVDV (SEQ ID NO: 3039)
1070A03	1732	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1070A09	1733	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1070B01	1734	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1070B05	1735	144 - 254	166 - 176	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	SQSDYDLTGYSGYGMVDV (SEQ ID NO: 3038)
1070D03	1736	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1070D04	1737	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1070E01	1738	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1070E09	1739	144 - 254	166 - 176	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	SQSDYDLTGYSGYGMVDV (SEQ ID NO: 3034)
1070F01	1740	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	SQSDYDLTGYSGYGMVDV (SEQ ID NO: 3038)
1070G10	1741	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1071A06	1742	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMVDV (SEQ ID NO: 2161)
1071B02	1743	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMVDV (SEQ ID NO: 2161)
1071D02	1744	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1071D08	1745	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 37	52 - 66	99 - 119	VPHYDYDTSGGYLGEYYGMVDV (SEQ ID NO: 3010)
1071F01	1746	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1071G09	1747	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSGYGMVDV (SEQ ID NO: 2153)
1072A01	1748	139 - 249	161 - 174	190 - 196	229 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDILLPHYGMVDV (SEQ ID NO: 2133)
1072A09	1749	141 - 248	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSGYGMVDV (SEQ ID NO: 2153)
1072B02	1750	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMVDV (SEQ ID NO: 2161)
1072B10	1751	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1072B11	1752	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSGYGMVDV (SEQ ID NO: 2153)
1072B12	1753	140 - 249	162 - 173	189 - 195	228 - 238	1 - 124	26 - 35	50 - 66	99 - 113	ENYDYDLTGYGAFDI (SEQ ID NO: 2995)
1072C05	1754	135 - 245	157 - 169	183 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMVDV (SEQ ID NO: 2161)
1072C10	1755	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSGYGMVDV (SEQ ID NO: 2153)
1072C01	1756	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSGYGMVDV (SEQ ID NO: 2153)
1072D05	1757	135 - 245	157 - 169	183 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMVDV (SEQ ID NO: 2161)

1072E01	1758	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1072E04	1759	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDILTYGVGVGRMDV (SEQ ID NO: 2171)
1072E05	1760	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1072E06	1761	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1072F03	1762	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO: 2161)
1072F07	1763	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1072F11	1764	400-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	DEYDILTLGLQGMVD (SEQ ID NO: 2883)
1072G03	1765	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1072G04	1766	137-247	159-171	187-193	226-236	1-121	26-35	50-66	101-110	RDLTGFDYS (SEQ ID NO: 2933)
1072G05	1767	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	GYRNDWYGAFEI (SEQ ID NO: 3079)
1072G09	1768	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1072H03	1769	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1072H07	1770	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGISLMNYGMDV (SEQ ID NO: 3070)
1073A02	1771	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	GPYDILTGYYRDAFDI (SEQ ID NO: 2998)
1073A03	1772	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	THYDILTGYYTADAFDI (SEQ ID NO: 3019)
1073A04	1773	148-258	170-183	199-205	238-247	1-132	26-35	50-66	99-121	VQMDSEYDILTGINVPYYDY (SEQ ID NO: 2132)
1073A05	1774	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073A06	1775	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073A09	1776	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073A10	1777	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-119	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073A11	1778	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	GFYDYLITGYVPYGMVD (SEQ ID NO: 3082)
1073B02	1779	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DLWYDILTGYYLDDAFDI (SEQ ID NO: 2999)
1073B05	1780	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DLWYDILTGYYLDDAFDI (SEQ ID NO: 2999)
1073B06	1781	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	SKDILLFPHYGMDV (SEQ ID NO: 2133)
1073B07	1782	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-114	TRMDVLTRYSDI (SEQ ID NO: 2750)
1073B08	1783	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073B11	1784	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073C01	1785	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	GYHDILTYSYNNWEPDI (SEQ ID NO: 3006)
1073C02	1786	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121	AQMDSEYDILTGINVPYYDY (SEQ ID NO: 3076)
1073C04	1787	141-252	164-177	193-199	232-241	1-128	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073C07	1788	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	GMGDHYMDV (SEQ ID NO: 3008)
1073C08	1789	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-114	EMGYDILTYGVLYNMDV (SEQ ID NO: 2862)
1073C09	1790	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	QHYDILTGYSQEPDI (SEQ ID NO: 3022)
1073C11	1791	146-256	168-181	197-203	236-245	1-130	26-35	50-68	101-119	FNPTYDILTGYYIGGYFOH (SEQ ID NO: 2155)
1073C12	1792	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
1073D01	1793	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)



variants thereof) that immunospecifically binds to BLyS; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject where BLyS is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody or fragment thereof above the background level and above or below the level observed in a person without the disease or disorder indicates that the subject has a particular disease or disorder associated with aberrant expression of BLyS or BLyS receptor. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

**[0384]** It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99</sup>Tc. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments," (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

**[0385]** Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

**[0386]** In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

**[0387]** Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the

invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

**[0388]** In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston *et al.*, U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

#### Immunophenotyping

**[0389]** The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be utilized for immunophenotyping of cell lines and biological samples by their BLyS expression or BLyS receptor expression. Various techniques can be utilized using antibodies, fragments, or variants of the invention to screen for cellular populations (*i.e.*, immune cells, particularly monocytic cells or B-cells) expressing BLyS or BLyS receptor, and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (*i.e.*, plate), and flow cytometry (see, *e.g.*, U.S. Patent 5,985,660; and Morrison *et al.*, Cell, 96:737-49 (1999)).

**[0390]** These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (*i.e.*, minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

**[0391]** In one embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) are used to identify cells of monocytic or B cell origin.

### Therapeutic Uses of Antibodies

**[0392]** The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies (and anti-idiotypic antibodies) of the invention as described herein. The antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of BLyS or BLyS receptor, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant BLyS expression and/or activity or aberrant BLyS receptor expression and/or activity includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

**[0393]** Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that function as agonists or antagonists of BLyS, preferably of BLyS-induced signal transduction, can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, lack of BLyS function, aberrant BLyS receptor expression, or lack of BLyS receptor function. For example, antibodies of the invention which disrupt the interaction between BLyS and its receptor may be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive of BLyS receptor function. Antibodies of the invention which do not prevent BLyS from binding its receptor but inhibit or downregulate BLyS-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function. In particular, antibodies of the present invention which prevent BLyS-induced signal transduction by specifically recognizing the unbound BLyS, receptor-bound BLyS or both unbound and receptor-bound BLyS can be

administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function. The ability of an antibody of the invention to inhibit or downregulate BLyS-induced signal transduction may be determined by techniques described herein or otherwise known in the art. For example, BLyS-induced receptor activation and the activation of signaling molecules can be determined by detecting the phosphorylation (*e.g.*, tyrosine or serine/threonine) of the receptor or a signaling molecule by immunoprecipitation followed by western blot analysis (for example, as described herein).

**[0394]** In a specific embodiment, an antibody of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that inhibits or downregulates BLyS activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to BLyS activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments, and/or variants that inhibit or downregulate BLyS activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to BLyS activity in absence of said antibodies, antibody fragments, and/or antibody variants are administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function.

**[0395]** Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which activate BLyS-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, lack of BLyS function, aberrant BLyS receptor expression, or lack of BLyS receptor function.

These antibodies may potentiate or activate either all or a subset of the biological activities of BLyS-mediated receptor activation, for example, by inducing multimerization of BLyS and/or multimerization of the receptor. The antibodies of the invention may be administered with or without being pre-complexed with BLyS. In a specific embodiment, an antibody of the present invention that increases BLyS activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to BLyS activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, lack of BLyS function, aberrant BLyS receptor expression, or lack of BLyS receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that increase BLyS activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to BLyS activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression or lack of BLyS function or aberrant BLyS receptor expression or lack of BLyS receptor function.

**[0396]** One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS may be used locally or systemically in the body as a therapeutic. The antibodies of this invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

**[0397]** The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered

alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or variants, (e.g., derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

**[0398]** It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLYS, or polynucleotides encoding antibodies that immunospecifically bind to BLYS, for both immunoassays directed to and therapy of disorders related to BLYS polynucleotides or polypeptides, including fragments thereof. Such antibodies will preferably have an affinity for BLYS and/or BLYS fragments. Preferred binding affinities include those with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M, or  $10^{-5}$  M. More preferably, antibodies of the invention bind BLYS polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M, or  $10^{-8}$  M. Even more preferably, antibodies of the invention bind BLYS polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M. The invention encompasses antibodies that bind BLYS polypeptides with a dissociation constant or  $K_D$  that is within any one of the ranges that are between each of the individual recited values.

**[0399]** In a preferred embodiment, antibodies of the invention neutralize BLYS activity. In another preferred embodiment, antibodies of the invention inhibit B cell proliferation.

**[0400]** In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of the soluble form of BLYS to a BLYS receptor. In another preferred embodiment antibodies of the invention inhibit or reduce B cell proliferation induced by the soluble form of BLYS. In another preferred embodiment

antibodies of the invention inhibit or reduce immunoglobulin production induced by the soluble form of BLyS.

**[0401]** In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of membrane-bound BLyS to a BLyS receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by the membrane-bound form of BLyS. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by the membrane bound form of BLyS.

**[0402]** In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of both the soluble and membrane-bound forms of BLyS to a BLyS receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by either or both forms of BLyS. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by either or both forms of BLyS.

**[0403]** In one embodiment, the invention provides a method of delivering antibody conjugates of the invention to targeted cells, such as, for example, monocytic cells expressing the membrane-bound form of BLyS, or B cells expressing a BLyS receptor.

**[0404]** In one embodiment, the invention provides a method for the specific delivery of antibodies and antibody conjugates of the invention to cells by administering molecules of the invention that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

**[0405]** In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs). In a specific embodiment, the invention provides a method for the specific destruction of cells of monocytic lineage (e.g., monocytic cell related

leukemias or lymphomas, such as, for example acute myelogenous leukemia) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that immunospecifically bind the membrane-bound form of BLyS. In another specific embodiment, the invention provides a method for the specific destruction of cells of B cell lineage (e.g., B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that bind soluble BLyS, but do not inhibit BLyS binding to a BLyS receptor on B cells.

**[0406]** In another preferred embodiment antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the soluble form of BLyS. In another preferred embodiment, antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the membrane or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the soluble form of BLyS. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the membrane bound or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production in response to T cell dependent immunogens. In another preferred embodiment antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance immunoglobulin production in response to T cell independent immunogens.

**[0407]** In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate immune disorders. Immune disorders include, but are not limited to, autoimmune disorders (e.g., arthritis, graft rejection, Hashimoto's thyroiditis, insulin-dependent diabetes, lupus, idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis), elective IgA deficiency, ataxia-telangiectasia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), Wiskott-



Aldrich syndrome, idiopathic hyper-eosinophilic syndrome, monocytic leukemoid reaction, monocytic leukocytosis, monocytic leukopenia, monocytopenia, monocytosis, and graft or transplant rejection.

**[0408]** As discussed herein, antibodies and antibody compositions of the invention, may be used to treat, prevent, ameliorate, diagnose or prognose various immune system-related disorders and/or conditions associated with these disorders, in mammals, preferably humans. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of antibody and antibody compositions of the invention that can inhibit an immune response, particularly the proliferation of B cells and/or the production of immunoglobulins, may be an effective therapy in treating and/or preventing autoimmune disorders. Thus, in preferred embodiments, antibodies and antibody compositions of the invention are used to treat, prevent, ameliorate, diagnose and/or prognose an autoimmune disorder, or condition(s) associated with such disorder.

**[0409]** Autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

**[0410]** Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis) (often characterized, e.g., by cell-mediated and humoral thyroid cytotoxicity), systemic lupus

erythematosus (often characterized, e.g., by circulating and locally generated immune complexes), discoid lupus, Goodpasture's syndrome (often characterized, e.g., by anti-basement membrane antibodies), Pemphigus (often characterized, e.g., by epidermal acantholytic antibodies), Receptor autoimmunities such as, for example, (a) Graves' Disease (often characterized, e.g., by TSH receptor antibodies), (b) Myasthenia Gravis (often characterized, e.g., by acetylcholine receptor antibodies), and (c) insulin resistance (often characterized, e.g., by insulin receptor antibodies), autoimmune hemolytic anemia (often characterized, e.g., by phagocytosis of antibody-sensitized RBCs), autoimmune thrombocytopenic purpura (often characterized, e.g., by phagocytosis of antibody-sensitized platelets).

**[0411]** Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis/dermatomyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes) such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjögren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies), chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often

characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), inflammatory myopathies, and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

**[0412]** In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, a member of the group: autoimmune hemolytic anemia, as primary glomerulonephritis, IgA glomerulonephritis, Goodpasture's syndrome, idiopathic thrombocytopenia, Multiple Sclerosis, Myasthenia Gravis, Pemphigus, polymyositis/dermatomyositis, relapsing polychondritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Uveitis, vasculitis, and primary biliary cirrhosis.

**[0413]** In another preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, an immune based-rheumatologic disease, such as, for example, SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), polymyositis/ dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder.

**[0414]** In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, rheumatoid arthritis and/or medical conditions associated therewith.

**[0415]** For example, an antibody, or antibodies, of the present invention are used to treat patients with clinical diagnosis of rheumatoid arthritis (RA). The patient treated preferably will not have a B cell malignancy. Moreover, the patient is optionally further treated with any one or more agents employed for treating RA such as salicylate; nonsteroidal anti-inflammatory drugs such as indomethacin, phenylbutazone, phenylacetic acid derivatives (e.g. ibuprofen and fenoprofen), naphthalene acetic acids (naproxen),

pyrrolealkanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, zomepirac and diflunisal; antimalarials such as chloroquine; gold salts; penicillamine; or immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages. Preferably however, the patient is only treated with an antibody, or antibodies, of the present invention. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. The primary response is determined by the Paulus index (Paulus et al. Arthritis Rheum. 33:477-484 (1990)), *i.e.* improvement in morning stiffness, number of painful and inflamed joints, erythrocyte sedimentation (ESR), and at least a 2-point improvement on a 5-point scale of disease severity assessed by patient and by physician. Administration of an antibody, or antibodies, of the present invention will alleviate one or more of the symptoms of RA in the patient treated as described above.

**[0416]** In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, lupus and/or medical conditions associated therewith. Lupus-associated conditions that may be treated, prevented, ameliorated, prognosed and/or diagnosed with the antibodies and antibody compositions of the invention include, but are not limited to, hematologic disorders (e.g., hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia), immunologic disorders (e.g., anti-DNA antibodies, and anti-Sm antibodies), rashes, photosensitivity, oral ulcers, arthritis, fever, fatigue, weight loss, serositis (e.g., pleuritis (pleurisy)), renal disorders (e.g., nephritis), neurological disorders (e.g., seizures, peripheral neuropathy, CNS related disorders), gastrointestinal disorders, Raynaud phenomenon, and pericarditis. In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, renal disorders associated with systemic lupus erythematosus. In a most preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, nephritis associated with systemic lupus erythematosus. In another most preferred embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate lupus or glomerular nephritis.

**[0417]** In a further specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent hemolytic anemia. For example, patients diagnosed with autoimmune hemolytic anemia (AIHA), *e.g.*, cryoglobulinemia or Coombs positive anemia, are treated with an antibody, or antibodies, of the present invention. AIHA is an acquired hemolytic anemia due to auto-antibodies that react with the patient's red blood cells. The patient treated preferably will not have a B cell malignancy. Further adjunct therapies (such as glucocorticoids, prednisone, azathioprine, cyclophosphamide, vinca-laden platelets or Danazol) may be combined with the antibody therapy, but preferably the patient is treated with an antibody, or antibodies, of the present invention as a single-agent throughout the course of therapy. Antibodies of the present invention are administered to the hemolytic anemia patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. Overall response rate is determined based upon an improvement in blood counts, decreased requirement for transfusions, improved hemoglobin levels and/or a decrease in the evidence of hemolysis as determined by standard chemical parameters. Administration of an antibody, or antibodies of the present invention will improve any one or more of the symptoms of hemolytic anemia in the patient treated as described above. For example, the patient treated as described above will show an increase in hemoglobin and an improvement in chemical parameters of hemolysis or return to normal as measured by serum lactic dehydrogenase and/or bilirubin.

**[0418]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Sjögren's Syndrome and/or medical conditions associated therewith.

**[0419]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, HIV infection and/or medical conditions associated therewith (*e.g.* AIDS).

**[0420]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Myasthenia gravis and/or medical conditions associated therewith.

**[0421]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, IgA nephropathy and/or medical conditions associated therewith.

**[0422]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, hemolytic anemia and/or medical conditions associated therewith.

**[0423]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, thyroiditis and/or medical conditions associated therewith.

**[0424]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Goodpasture's Syndrome and/or medical conditions associated therewith.

**[0425]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple sclerosis and/or medical conditions associated therewith.

**[0426]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, chronic lymphocytic leukemia (CLL) and/or medical conditions associated therewith.

**[0427]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple myeloma and/or medical conditions associated therewith.

**[0428]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Non-Hodgkin's lymphoma and/or medical conditions associated therewith.

**[0429]** In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Hodgkin's disease and/or medical conditions associated therewith.

**[0430]** In another specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent adult immune thrombocytopenic purpura. Adult immune thrombocytopenic purpura (ITP) is a relatively rare hematologic disorder that constitutes the most common of the immune-mediated cytopenias. The disease typically presents with severe thrombocytopenia that may be associated with acute hemorrhage in the presence of normal to increased megakaryocytes in the bone marrow. Most patients with ITP have an IgG antibody directed against target antigens on the outer surface of the platelet membrane, resulting in platelet sequestration in the spleen and

accelerated reticuloendothelial destruction of platelets (Bussell, J.B. Hematol. Oncol. Clin. North Am. (4):179 (1990)). A number of therapeutic interventions have been shown to be effective in the treatment of ITP. Steroids are generally considered first-line therapy, after which most patients are candidates for intravenous immunoglobulin (IVIG), splenectomy, or other medical therapies including vincristine or immunosuppressive/cytotoxic agents. Up to 80% of patients with ITP initially respond to a course of steroids, but far fewer have complete and lasting remissions. Splenectomy has been recommended as standard second-line therapy for steroid failures, and leads to prolonged remission in nearly 60% of cases yet may result in reduced immunity to infection. Splenectomy is a major surgical procedure that may be associated with substantial morbidity (15%) and mortality (2%). IVIG has also been used as second line medical therapy, although only a small proportion of adult patients with ITP achieve remission. Therapeutic options that would interfere with the production of autoantibodies by activated B cells without the associated morbidities that occur with corticosteroids and/or splenectomy would provide an important treatment approach for a proportion of patients with ITP. Patients with clinical diagnosis of ITP are treated with an antibody, or antibodies of the present invention, optionally in combination with steroid therapy. The patient treated will not have a B cell malignancy. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. Overall patient response rate is determined based upon a platelet count determined on two consecutive occasions two weeks apart following treatments as described above. See, George et al. "Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology", Blood 88:3-40 (1996), expressly incorporated herein by reference.

**[0431]** In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate an IgE-mediated allergic reaction or histamine-mediated allergic reaction. Examples of allergic reactions include, but are not limited to, asthma, rhinitis, eczema, chronic urticaria, and atopic dermatitis. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent, or ameliorate anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility. In another embodiment, therapeutic or pharmaceutical compositions of the invention are

administered to an animal to treat, prevent or ameliorate or modulate inflammation or an inflammatory disorder. Examples of chronic and acute inflammatory disorders that may be treated prevented or ameliorated with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, Crohn's disease, inflammatory bowel disease, chronic and acute inflammatory pulmonary diseases, bacterial infection, psoriasis, septicemia, cerebral malaria, arthritis, gastroenteritis, and glomerular nephritis.

**[0432]** In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate ischemia and arteriosclerosis. Examples of such disorders include, but are not limited to, reperfusion damage (e.g., in the heart and/or brain) and cardiac hypertrophy.

**[0433]** Therapeutic or pharmaceutical compositions of the invention, may also be administered to modulate blood clotting and to treat or prevent blood clotting disorders, such as, for example, antibody-mediated thrombosis (i.e., antiphospholipid antibody syndrome (APS)). For example, therapeutic or pharmaceutical compositions of the invention, may inhibit the proliferation and differentiation of cells involved in producing anticardiolipin antibodies. These compositions of the invention can be used to treat, prevent, ameliorate, diagnose, and/or prognose thrombotic related events including, but not limited to, stroke (and recurrent stroke), heart attack, deep vein thrombosis, pulmonary embolism, myocardial infarction, coronary artery disease (e.g., antibody-mediated coronary artery disease), thrombosis, graft reocclusion following cardiovascular surgery (e.g., coronary arterial bypass grafts, recurrent fetal loss, and recurrent cardiovascular thromboembolic events).

**[0434]** Therapeutic or pharmaceutical compositions of the invention, may also be administered to treat, prevent, or ameliorate organ rejection or graft-versus-host disease (GVHD) and/or conditions associated therewith. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of antibodies of the invention,



that inhibit an immune response, may be an effective therapy in preventing organ rejection or GVHD.

**[0435]** In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate a disease or disorder diseases associated with increased apoptosis including, but not limited to, AIDS, neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration), myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate bone marrow failure, for example, aplastic anemia and myelodysplastic syndrome.

**[0436]** In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate growth, progression, and/or metastases of malignancies and proliferative disorders associated with increased cell survival, or the inhibition of apoptosis. Examples of such disorders, include, but are not limited to, leukemia (*e.g.*, acute leukemia such as acute lymphocytic leukemia and acute myelocytic leukemia), neoplasms, tumors (*e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma), heavy chain disease, metastases, or any disease or disorder characterized by uncontrolled cell growth.

**[0437]** In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies).

**[0438]** In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, therapeutic or pharmaceutical compositions of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

**[0439]** Therapeutic or pharmaceutical compositions of the invention of the invention thereof, may be used to diagnose, prognose, treat or prevent one or more of the following diseases or disorders, or conditions associated therewith: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, bone marrow transplant (e.g., recent bone marrow transplant in adults or children), chronic B-cell lymphocytic leukemia, HIV infection (e.g., adult or pediatric HIV infection), chronic inflammatory demyelinating polyneuropathy, and post-transfusion purpura.

**[0440]** Additionally, therapeutic or pharmaceutical compositions of the invention may be used to diagnose, prognose, treat or prevent one or more of the following diseases, disorders, or conditions associated therewith, Guillain-Barre syndrome, anemia (e.g., anemia associated with parvovirus B19, patients with stable multiple myeloma who are at high risk for infection (e.g., recurrent infection), autoimmune hemolytic anemia (e.g., warm-type autoimmune hemolytic anemia), thrombocytopenia (e.g., neonatal thrombocytopenia), and immune-mediated neutropenia), transplantation (e.g., cytomegalovirus (CMV)-negative recipients of CMV-positive organs), hypogammaglobulinemia (e.g., hypogammaglobulinemic neonates with risk factor for

infection or morbidity), epilepsy (e.g., intractable epilepsy), systemic vasculitic syndromes, myasthenia gravis (e.g., decompensation in myasthenia gravis), dermatomyositis, and polymyositis.

**[0441]** Additional preferred embodiments of the invention include, but are not limited to, the use of therapeutic or pharmaceutical compositions of the invention in the following applications:

**[0442]** Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response. In a specific nonexclusive embodiment, therapeutic or pharmaceutical compositions of the invention are administered to boost the immune system to produce increased quantities of IgG. In another specific nonexclusive embodiment, antibodies of the are administered to boost the immune system to produce increased quantities of IgA. In another specific nonexclusive embodiment antibodies of the invention are administered to boost the immune system to produce increased quantities of IgM.

**[0443]** Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).

**[0444]** In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a vaccine adjuvant that enhances immune responsiveness to specific antigen. In a specific embodiment, the vaccine is an antibody described herein. In another specific embodiment, the vaccine adjuvant is a polynucleotide described herein (e.g., an antibody polynucleotide genetic vaccine adjuvant). As discussed herein, therapeutic or pharmaceutical compositions of the invention may be administered using techniques known in the art, including but not limited to, liposomal delivery, recombinant vector delivery, injection of naked DNA, and gene gun delivery.

**[0445]** In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance tumor-specific immune responses.

**[0446]** In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include, but are not limited to, virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to the HIV gp120 antigen.

**[0447]** In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella* spp., Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and *Plasmodium* (malaria).

**[0448]** In a specific embodiment, therapeutic or pharmaceutical compositions of

1076G01	1865	143-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	VEGVYDILTGYSFDAFDI (SEQ ID NO: 3078)
1076H01	1866	144-250	168-178	194-200	233-243	1-128	26-35	50-66	99-117	EQGYDILTGYPGGWFDP (SEQ ID NO: 2834)
1076H03	1867	140-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELGSVNGATTGALDM (SEQ ID NO: 2174)
1077B05	1868	147-257	169-182	198-204	237-246	1-131	26-37	52-69	102-120	DKSYYDILTGYYGYGMDV (SEQ ID NO: 3052)
1077C10	1869	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077D01	1870	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077D04	1871	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077D11	1872	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077D12	1873	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	EKYDILTGYYDAFDI (SEQ ID NO: 3046)
1077E01	1874	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	EMGYDILTGYYLNMYDM (SEQ ID NO: 2862)
1077E08	1876	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077F05	1877	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077G06	1878	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1077H02	1879	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1078B05	1880	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1079E02	1881	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ESHYDILTGYYNSPFDI (SEQ ID NO: 2994)
1079F11	1882	132-239	155-165	181-187	220-228	1-116	26-35	50-66	99-110	DCSGYYDAFDI (SEQ ID NO: 2194)
1082G02	1883	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-105	TCSGFDY (SEQ ID NO: 2192)
1082H08	1884	131-242	154-167	183-189	222-231	1-115	26-35	50-66	99-109	DGYRTNDALDI (SEQ ID NO: 2191)
1099D03	1885	136-247	159-172	188-194	227-236	1-120	26-35	50-66	99-104	DWDMDV (SEQ ID NO: 2193)
1079B05	1886	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-109	DNGGGTGFYD (SEQ ID NO: 2195)
1079B12	1887	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	FVLDY (SEQ ID NO: 2210)
1079C01	1888	131-241	153-166	182-188	221-230	1-115	26-35	50-66	99-107	WTSSGAFDI (SEQ ID NO: 2205)
1079F06	1889	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-104	DWDMDV (SEQ ID NO: 2193)
1079F08	1890	138-248	160-172	188-194	227-237	1-122	26-35	50-66	99-107	DNLHAAFDI (SEQ ID NO: 2202)
1080A03	1891	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	YYYHSSGDAFDI (SEQ ID NO: 2206)
1080A08	1892	135-240	158-171	187-193	226-236	1-119	26-35	50-66	99-111	VGKAAAADFNEY (SEQ ID NO: 2197)
1080B01	1893	142-254	166-178	194-200	233-243	1-126	26-35	50-66	99-108	VHSTGYAFEN (SEQ ID NO: 2200)
1080D03	1894	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-115	EVSQHYHVEGGSYAMDV (SEQ ID NO: 2201)
1080E05	1895	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	VGKAAAADFNEY (SEQ ID NO: 2197)
1080G07	1896	136-245	161-172	188-194	227-234	1-120	26-35	50-66	99-114	EGGGDAYDAPYTFYD (SEQ ID NO: 2204)
1080G09	1897	136-249	159-172	188-194	227-238	1-120	26-35	50-66	99-109	EGRGYYGYGMDV (SEQ ID NO: 2209)
1082A05	1898	131-240	153-165	181-187	220-229	1-115	26-35	50-66	99-109	DNGGGTGFYD (SEQ ID NO: 2195)
1082B08	1899	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-104	DLDPDFY (SEQ ID NO: 2208)
1082C03	1900	138-245	161-171	187-193	226-234	1-122	26-35	50-66	99-111	DASRDIVVLPLAI (SEQ ID NO: 2198)

1082D07	1901	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	WTSSGAFDI (SEQ ID NO: 2205)
1082G01	1902	138-245	161-171	187-193	226-234	1-122	26-35	50-66	99-111	DRSGWPNTYFDL (SEQ ID NO: 2212)
1083B02	1903	137-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110	ESGAGYYDDY (SEQ ID NO: 2196)
1083G13	1904	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	VGKAAAYDNFEY (SEQ ID NO: 2197)
1084A01	1905	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
1084B02	1906	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
1084C04	1907	131-238	152-162	178-184	217-227	1-115	25-34	49-65	98-104	NLWGLDY (SEQ ID NO: 2199)
1084C11	1908	134-244	156-168	185-191	224-233	1-118	26-35	50-66	99-107	GNAGWAFDI (SEQ ID NO: 2211)
1079A01	1909	134-243	156-168	184-190	223-231	1-118	26-35	50-66	99-107	EGVAAGEDY (SEQ ID NO: 3123)
1079A03	1910	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	GGMDWDFDY (SEQ ID NO: 3183)
1079A04	1911	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	VDSGGYAY (SEQ ID NO: 3213)
1079A06	1912	133-240	154-164	180-186	219-229	1-117	26-35	50-66	99-106	DAANTAE (SEQ ID NO: 3142)
1079A07	1913	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109	GNYSPPAFDI (SEQ ID NO: 3112)
1079A10	1914	148-255	169-179	195-201	234-244	1-132	26-35	50-68	101-121	LPDLRYCDGGICPGDWLGP (SEQ ID NO: 3163)
1079A11	1915	135-242	158-168	184-190	223-231	1-119	26-35	50-66	99-108	GFYSYYMAV (SEQ ID NO: 3114)
1079B02	1916	134-243	156-168	184-190	223-232	1-118	26-35	50-66	99-107	EGVAAGEDY (SEQ ID NO: 3123)
1079B03	1917	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109	GNYSPPAFDI (SEQ ID NO: 3112)
1079B04	1918	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	LLSDY (SEQ ID NO: 3168)
1079B07	1919	138-245	159-169	185-191	224-234	1-122	26-35	50-66	99-111	DLSGYSRFDY (SEQ ID NO: 3193)
1079B09	1920	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-112	VEVEDIVVGSAPDI (SEQ ID NO: 3128)
1079C02	1921	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117	VTSLYSSSGYGGYGGMDV (SEQ ID NO: 3145)
1079C04	1922	132-239	155-165	181-187	220-228	1-116	26-35	50-66	99-105	GWRGVY (SEQ ID NO: 3195)
1079C05	1923	140-247	163-173	188-195	228-236	1-124	26-35	50-66	99-113	AGGNPRSGSLYFDY (SEQ ID NO: 3225)
1079C07	1924	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	GLDVYAYGLDV (SEQ ID NO: 3176)
1079D01	1925	144-254	166-176	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLTRSYLAGPLDN (SEQ ID NO: 2751)
1079D02	1926	135-242	157-169	185-191	224-234	1-119	26-35	50-66	99-108	EGWEGAFDI (SEQ ID NO: 3178)
1079D04	1927	133-243	155-167	183-189	222-232	1-117	26-35	50-66	99-106	VRPGLMDV (SEQ ID NO: 3132)
1079D06	1928	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	EAYTSSWAEFDF (SEQ ID NO: 3190)
1079D07	1929	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	NITPLAMWGDF (SEQ ID NO: 3146)
1079D08	1930	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	LIEDF (SEQ ID NO: 3161)
1079D09	1931	131-238	152-162	178-184	217-227	1-115	26-35	50-66	99-104	DSGSPD (SEQ ID NO: 3108)
1079D11	1932	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	EGVAAGEDY (SEQ ID NO: 3123)
1079E06	1933	136-244	158-168	184-190	223-233	1-120	26-35	50-66	99-109	EKRGSRVFDY (SEQ ID NO: 3093)
1079E08	1934	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	EAYASSWAEFDF (SEQ ID NO: 3189)
1079E11	1935	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	PYGSGAFDI (SEQ ID NO: 3185)
1079E12	1936	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116	ARDYYDSSGGYVPDAFDI (SEQ ID NO: 3107)

1937	133-241	154-164	180-186	219-230	1-117	26-35	50-66	99-106	GHEYGMV (SEQ ID NO: 3098)
1938	148-253	169-179	195-201	234-242	1-132	26-35	50-68	101-121	LPPLRYCDGCMCSGFWDLP (SEQ ID NO: 3219)
1939	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-103	ESLITEEYCSDCYS (SEQ ID NO: 3115)
1940	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-119	NSAPAPSMV (SEQ ID NO: 3099)
1941	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103	RTYVD (SEQ ID NO: 3139)
1942	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	NITPLAMVGF (SEQ ID NO: 3146)
1943	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	ADYSDNYMDV (SEQ ID NO: 3146)
1944	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	NITPLAMVGF (SEQ ID NO: 3146)
1945	136-243	159-169	183-191	224-232	1-120	26-35	50-66	99-109	FPLEYSYMDV (SEQ ID NO: 3124)
1946	135-245	157-167	180-192	225-234	1-119	26-35	50-66	99-108	GNSFGKTLV (SEQ ID NO: 3158)
1947	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	DVPPDGYLEV (SEQ ID NO: 3192)
1948	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	ASYVPFV (SEQ ID NO: 3171)
1949	131-242	154-166	183-188	221-231	1-115	26-35	50-66	99-104	GGWLDD (SEQ ID NO: 3210)
1950	133-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106	EHSSFDY (SEQ ID NO: 3111)
1951	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	EGEGDYNVAPYFDY (SEQ ID NO: 3160)
1952	141-250	166-176	192-198	231-239	1-125	26-35	50-66	99-114	EAGSGSVHSPFDY (SEQ ID NO: 3188)
1953	135-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108	TGWLGYFDY (SEQ ID NO: 3175)
1954	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	DGNLNYDGSYDGMV (SEQ ID NO: 3140)
1955	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	LGRNYTSSWLDY (SEQ ID NO: 3181)
1956	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-110	VGGYSSLTGTDY (SEQ ID NO: 3096)
1957	137-249	161-173	189-195	228-238	1-121	26-35	50-66	99-110	LGVARGREAFD (SEQ ID NO: 3206)
1958	142-254	165-177	193-199	232-243	1-126	26-37	52-69	102-115	AVRSPGYYYMDV (SEQ ID NO: 3125)
1959	133-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106	GRKPLFDY (SEQ ID NO: 3141)
1960	136-248	159-172	188-194	227-237	1-120	26-37	52-67	100-109	KQRREYFDY (SEQ ID NO: 3100)
1961	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	EKAIETTSGEADPDI (SEQ ID NO: 3151)
1962	138-249	161-173	189-195	228-238	1-122	26-37	52-67	100-111	RPALRSLWYFDL (SEQ ID NO: 3102)
1963	137-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110	LHCTGGSCGF (SEQ ID NO: 3186)
1964	139-253	164-179	195-201	234-242	1-123	26-35	50-66	99-112	NPYYSDSSEGFY (SEQ ID NO: 3109)
1965	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SCRQAYYYGMDV (SEQ ID NO: 3091)
1966	144-254	168-178	194-200	233-243	1-128	26-36	51-66	99-117	DYDGSYSSGSDYYMDV (SEQ ID NO: 3227)
1967	144-256	167-180	196-202	235-245	1-128	26-35	50-66	99-117	DSDLVVIPTAQGRYFDN (SEQ ID NO: 3113)
1968	137-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110	GRKSYGWYFDI (SEQ ID NO: 3130)
1969	131-243	154-167	183-189	222-232	1-115	26-35	50-66	99-104	DTPLDP (SEQ ID NO: 3094)
1970	137-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110	EGDPTDNDAPDV (SEQ ID NO: 3155)
1971	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	DGPTYARPYLDH (SEQ ID NO: 3153)
1972	136-245	161-171	187-193	226-234	1-120	26-35	50-66	99-109	DGTYKVDWGFY (SEQ ID NO: 3220)

1080D02	1973	141-254	164-177	193-199	232-243	1-125	26-35	50-66	99-114	ETFSHCSGSGYPEDY (SEQ ID NO: 3212)
1080D04	1974	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SCRQAYYYGYMDV (SEQ ID NO: 3091)
1080D05	1975	136-246	160-170	186-192	225-235	1-120	26-35	50-66	99-109	EFFGVYLTIDY (SEQ ID NO: 3165)
1080D08	1976	137-248	160-172	188-194	227-237	1-121	26-35	50-66	101-110	LHCTGSGGCF (SEQ ID NO: 3186)
1080D09	1977	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	VYTDYEMGAFEI (SEQ ID NO: 3187)
1080D11	1978	135-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108	VGNFYGYTEY (SEQ ID NO: 3196)
1080D12	1979	135-245	159-169	185-191	224-234	1-119	26-35	50-66	101-108	SSRNGGDY (SEQ ID NO: 3144)
1080E01	1980	136-246	160-170	186-192	225-235	1-120	26-35	50-66	99-109	DLRSVAGRPDY (SEQ ID NO: 3164)
1080E04	1981	136-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109	HDVYGLDFDY (SEQ ID NO: 3211)
1080E06	1982	137-248	160-172	188-194	227-237	1-121	26-35	50-66	101-110	LHCSGSGGCF (SEQ ID NO: 3221)
1080E07	1983	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	EGSIVGATLTINDAFDI (SEQ ID NO: 3150)
1080E08	1984	137-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110	GKRYSGWYFDI (SEQ ID NO: 3130)
1080E12	1985	130-242	154-166	182-188	221-231	1-114	26-35	50-66	99-103	DPFDY (SEQ ID NO: 3134)
1080F04	1986	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	DGPTYARPYLDH (SEQ ID NO: 3153)
1080F05	1987	142-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	ESSGTLGEFSLPFDY (SEQ ID NO: 3203)
1080F06	1988	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	LGRNVTSSWSLDY (SEQ ID NO: 3181)
1080F08	1989	130-240	154-164	180-186	219-229	1-114	26-35	50-66	99-103	NAFDY (SEQ ID NO: 3121)
1080G03	1990	140-250	164-174	190-196	229-239	1-124	26-36	51-66	99-113	GRGYSSSSVYGMDI (SEQ ID NO: 3095)
1080G04	1991	131-244	156-171	187-193	226-233	1-115	26-35	50-66	99-104	VHSSGS (SEQ ID NO: 3216)
1080G10	1992	143-252	167-177	193-199	232-241	1-127	26-35	50-66	99-116	KRGDFGVIRLHHYYGMDV (SEQ ID NO: 3136)
1080G11	1993	136-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109	HDVYGLDFDS (SEQ ID NO: 3205)
1080H01	1994	140-252	164-176	192-198	231-241	1-124	26-37	52-67	100-113	LRPDADYGDYGFY (SEQ ID NO: 3218)
1080H02	1995	139-248	162-172	188-194	227-237	1-123	26-35	50-66	99-112	TSERGTYROWDFDN (SEQ ID NO: 3204)
1080H03	1996	135-246	158-170	186-192	225-235	1-119	26-35	50-66	99-108	EAGEVAADY (SEQ ID NO: 3180)
1080H04	1997	137-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110	GKRYSGWYFDI (SEQ ID NO: 3130)
1080H05	1998	136-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109	HDVYGLDFDS (SEQ ID NO: 3205)
1080H06	1999	137-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110	GKRYSGWYFDY (SEQ ID NO: 3217)
1080H07	2000	137-248	160-172	188-194	227-237	1-121	26-35	50-66	101-110	LHCTGSGGCF (SEQ ID NO: 3186)
1080H08	2001	138-251	162-175	191-197	230-240	1-122	26-35	50-66	99-111	ERGRDGDYALDF (SEQ ID NO: 3148)
1080H09	2002	139-249	163-173	189-195	228-238	1-123	26-36	51-66	99-112	RTPDHNGDSGPPDY (SEQ ID NO: 3215)
1081A01	2003	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081A03	2004	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	ESLTTGGAFDI (SEQ ID NO: 3117)
1081A04	2005	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081A06	2006	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081A08	2007	130-240	152-164	180-186	219-229	1-118	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081A09	2008	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	GAGSKYFDL (SEQ ID NO: 3118)



1081A10	2009	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106	GGDRAFDI (SEQ ID NO: 3119)
1081B01	2010	130-236	151-161	177-183	216-225	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081B04	2011	134-244	156-169	185-191	224-232	1-117	26-35	50-66	99-107	GNAGGAFDI (SEQ ID NO: 2211)
1081B05	2012	133-243	155-168	184-190	223-232	1-118	26-35	50-66	99-106	GGDRAFDI (SEQ ID NO: 3119)
1081B06	2013	133-240	154-164	180-186	219-229	1-117	26-35	50-66	99-106	VKRYEDY (SEQ ID NO: 3179)
1081B07	2014	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	ELTGANDAFDI (SEQ ID NO: 3104)
1081B08	2015	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105	RRYALDY (SEQ ID NO: 2920)
1081B09	2016	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081B10	2017	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081B11	2018	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105	GFALYKD (SEQ ID NO: 3169)
1081C07	2019	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081C08	2020	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081D04	2021	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	ELTGDAFDI (SEQ ID NO: 3103)
1081D06	2022	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105	GDAYFDY (SEQ ID NO: 3147)
1081D08	2023	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105	GDAYFDY (SEQ ID NO: 3147)
1081D09	2024	130-238	152-162	178-184	217-227	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081D10	2025	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081D11	2026	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	EGLIDAFDI (SEQ ID NO: 3200)
1081D12	2027	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081E02	2028	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081E03	2029	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081E05	2030	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081E06	2031	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	VGYGKGDY (SEQ ID NO: 3137)
1081E07	2032	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	GAGRYFDL (SEQ ID NO: 3118)
1081E10	2033	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	GLAPIVDGGMINDAFDI (SEQ ID NO: 3184)
1081F01	2034	130-239	152-164	180-186	219-228	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081F04	2035	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-103	RLIKAR (SEQ ID NO: 3170)
1081F05	2036	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081F06	2037	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	ERGNQAFDI (SEQ ID NO: 3156)
1081F07	2038	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105	RRYALDY (SEQ ID NO: 2920)
1081F11	2039	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081G01	2040	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081G04	2041	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081G06	2042	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	SKSPYDAFDI (SEQ ID NO: 3097)
1081G10	2043	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081G12	2044	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)

1081H03	2045	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1081H04	2046	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	SNWGGDAFDI (SEQ ID NO: 3202)
1081H06	2047	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	LAFDI (SEQ ID NO: 3174)
1081H08	2048	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1082A02	2049	139-240	161-173	189-195	228-238	1-123	26-35	50-66	99-112	PAASRRGPKDAFDI (SEQ ID NO: 3129)
1082A04	2050	139-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	LSGDS (SEQ ID NO: 3122)
1082A08	2051	134-243	156-168	184-190	223-232	1-118	26-35	50-66	99-107	EGVAAAGEDY (SEQ ID NO: 3123)
1082A11	2052	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	FVLIDY (SEQ ID NO: 2210)
1082B06	2053	131-238	154-164	180-186	219-227	1-115	26-35	50-66	99-104	GNGKDY (SEQ ID NO: 3135)
1082B09	2054	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	EGVAAAGEDY (SEQ ID NO: 3123)
1082B12	2055	131-241	153-166	182-188	221-230	1-115	26-35	50-66	99-104	DLDFFDY (SEQ ID NO: 2208)
1082C01	2056	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	VNDIVVVDMDV (SEQ ID NO: 3143)
1082C05	2057	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	EKRGRRVFDI (SEQ ID NO: 3095)
1082C08	2058	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	LSNRNDNLRLDY (SEQ ID NO: 3106)
1082D02	2059	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	FVLIDY (SEQ ID NO: 2210)
1082E05	2060	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	TWATNIFDM (SEQ ID NO: 3152)
1082E06	2061	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	FLLDY (SEQ ID NO: 3167)
1082E07	2062	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-112	VEVEDIVVGSADF (SEQ ID NO: 3128)
1082F11	2063	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	GGDMITVTIDY (SEQ ID NO: 3177)
1082G07	2064	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	ADYSNDYMDV (SEQ ID NO: 3166)
1082G10	2065	134-249	160-173	189-195	228-238	1-118	26-35	50-66	99-107	EGVAAAGEDY (SEQ ID NO: 3123)
1082G11	2066	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	GPVYFDGSAYEGYTDY (SEQ ID NO: 3222)
1082H04	2067	132-238	153-163	179-185	218-227	1-116	26-35	50-65	98-105	MNADAFEI (SEQ ID NO: 3223)
1082H09	2068	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	PAASRRGPKDAFDI (SEQ ID NO: 3129)
1083A06	2069	136-244	159-169	185-191	224-233	1-120	26-35	50-66	99-109	DSRPTNRAFDY (SEQ ID NO: 3110)
1083A09	2070	137-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110	LHCTGGSCGF (SEQ ID NO: 3186)
1083A11	2071	135-248	158-171	187-193	226-237	1-119	26-35	50-66	99-108	VRDSDAGFDY (SEQ ID NO: 3173)
1083B03	2072	137-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110	VLVRYGVRGMDL (SEQ ID NO: 3138)
1083B05	2073	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	VDYTYEMGAFDL (SEQ ID NO: 3172)
1083B06	2074	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	DRAAAGDAFDI (SEQ ID NO: 3194)
1083B10	2075	137-246	162-172	188-194	227-235	1-121	26-35	50-66	99-110	DLYKNGYALFDS (SEQ ID NO: 3197)
1083C01	2076	135-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108	DEYSSLYMDY (SEQ ID NO: 3201)
1083C02	2077	135-246	158-171	187-193	226-235	1-119	26-35	50-66	99-108	FGAGRLYDDY (SEQ ID NO: 3204)
1083C07	2078	136-249	159-172	188-194	227-238	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO: 2195)
1083C12	2079	135-246	158-171	187-193	226-235	1-119	26-35	50-66	99-108	DQGIETANDY (SEQ ID NO: 3207)
1083D04	2080	145-256	168-181	197-203	226-235	1-129	26-35	50-66	99-118	DILPYDFWNPNEASSLDT (SEQ ID NO: 3133)

1083D07	2081	148-262	173-188	204-210	243-251	1-132	26-35	50-66	99-121	DFQVMRGVFIANPPIYNYGMDV (SEQ ID NO: 3154)
1083D08	2082	142-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	DADEGLVEAETTNWFDs (SEQ ID NO: 3126)
1083D10	2083	146-258	169-181	197-203	236-247	1-130	26-37	52-69	102-119	ATKSYDLTRMYHYHMDV (SEQ ID NO: 2748)
1083D12	2084	132-242	156-166	182-188	221-231	1-116	26-35	50-66	99-105	DKTRMDV (SEQ ID NO: 3182)
1083E02	2085	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	VGKAAAADNFEY (SEQ ID NO: 2197)
1083E03	2086	135-248	158-171	187-193	226-237	1-119	26-35	50-66	99-108	DEYNDAFDY (SEQ ID NO: 3105)
1083E04	2087	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	DGDISDPINNQNAYAMD (SEQ ID NO: 3101)
1083E08	2088	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	RGTSENTSGMDV (SEQ ID NO: 3209)
1083E12	2089	134-245	157-170	186-192	225-234	1-118	26-35	50-66	99-107	DYPHNAFD (SEQ ID NO: 3127)
1083F02	2090	145-258	168-181	197-203	236-247	1-129	26-35	50-66	99-118	DVSRDFWSGGVHYHSGMDV (SEQ ID NO: 3131)
1083F04	2091	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	STLEVGATDFDY (SEQ ID NO: 3199)
1083F06	2092	134-247	157-170	186-192	225-236	1-118	26-35	50-66	99-107	SDDWGAYHI (SEQ ID NO: 3198)
1083F08	2093	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	ERGRDGDYALDF (SEQ ID NO: 3148)
1083F11	2094	136-248	159-172	188-194	227-237	1-120	26-35	50-66	99-109	ELVGAPGGDF (SEQ ID NO: 3191)
1083G04	2095	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	VDYTDYEMGATDL (SEQ ID NO: 3172)
1083G05	2096	137-249	161-173	189-195	228-238	1-121	26-35	50-68	101-110	SVAGRGNDY (SEQ ID NO: 3208)
1083G06	2097	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	ERGRDGDYALDF (SEQ ID NO: 3148)
1083G08	2098	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	EGGDAYDYAPYFDY (SEQ ID NO: 2204)
1083G09	2099	130-242	154-166	182-188	221-231	1-114	26-35	50-66	99-103	DPFDY (SEQ ID NO: 3134)
1083G11	2100	140-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	ALLGLPSDFSYVDV (SEQ ID NO: 3159)
1083H04	2101	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	EGEGDGYNAPYFDY (SEQ ID NO: 3160)
1083H05	2102	133-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106	TDYGGFDY (SEQ ID NO: 3092)
1083H07	2103	137-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110	GVGDSRGVDFP (SEQ ID NO: 3162)
1084A03	2104	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084A08	2105	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084B08	2106	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084C02	2107	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-108	ESLTGDAFDI (SEQ ID NO: 3116)
1084D03	2108	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-109	SLPHSDAFDI (SEQ ID NO: 3120)
1084D05	2109	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084E01	2110	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-106	EVGGAFDI (SEQ ID NO: 3157)
1084E06	2111	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084E10	2112	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084E12	2113	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084F04	2114	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084F07	2115	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO: 2203)
1084F12	2116	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	ESLTGDAFDI (SEQ ID NO: 3116)

1084G12	2117	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1084H02	2118	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTIDY (SEQ ID NO: 2203)
1099B05	2119	145-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118	GAHYDRSPSHLSKYWYFDL (SEQ ID NO: 3149)
1099G09	2120	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	VGKAAAVDNEFY (SEQ ID NO: 2197)
1099H01	2121	138-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	LGRNYTSSWLDY (SEQ ID NO: 3181)
1099H06	2122	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	VGKAAAVDNEFY (SEQ ID NO: 2197)
1099H08	2123	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	GRYGYYYDGTGYVDADI (SEQ ID NO: 3226)
1100A01	2124	136-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO: 2195)
1100A10	2125	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	VRQIADPPRSFDF (SEQ ID NO: 3144)
1100B03	2126	136-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO: 2195)
1100B04	2127	136-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO: 2195)
1100C03	2128	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	VRQIADPPRSFDF (SEQ ID NO: 3144)